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WEIGHT AND PHYSICAL MEASUREMENTS AFTER THYROIDECTOMY

RAPID CHANGES IN WEIGHT REFLECTED IN PHYSICAL MEASUREMENTS ON ADULTS AFTER THYROIDECTOMY *

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CONSTANCY OF AN ADULT'S BODY WEIGHT

Body weight during adult life is constant to a noteworthy degree, notwithstanding the fluctuations which occur during physical exercise and the variations in the diet.[1] As yet few people follow the regimen of the person who has been treated for diabetes, who weighs or tries to estimate carefully the portions of food taken, even though the country does show signs of becoming calorie conscious. Man normally eats what he wants, and as much as he wants if he can get it. Nevertheless, it is more than common to hear such expressions as, "I have hardly gained or lost a pound in the last fifteen years," or, what is slightly more an exact self-observation, "I have gained only a little and that very slowly." This fair constancy of the individual is in contrast with the wide variations in weight shown by the different men and women in any large group that may be measured.

VARIABILITY OF WEIGHT COMPARED WITH OTHER BODY MEASUREMENTS

Of all the gross physical measurements frequently made, that of body weight gives the greatest variability within the group. This is to be expected, as weight is a cubic measure whereas the others are linear or cross-sectional measures. The range found in weight for a thousand men cannot be compared directly with the range found for stature in the same persons. The units are not of the same kind. To secure a

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1. DuBois, Eugene, F.: Basal Metabolism in Health and Disease, Philadelphia, Lea and Febiger, 1924, p. 181.

basis for direct comparison is, however, a simple matter. It is necessary to find only the average variation, or better the standard deviation, for the series of weights and to divide this by the average or mean weight for the group. A similar computation is made for the measurements of weight. Then there are two so-called "coefficients of variation" which are given in terms of percentage and freed from the original units of measurement.

For a better understanding of such comparisons and their importance, we may refer to extensive data published by Davenport and Love.[2] We include in table 1 a simplified revision of a table in which they give a summary of dimensions of approximately 100,000 white troops at demobilization in 1919. In this table it will be found that the extreme coefficients are those for height and weight, 3.9 and 11.7 per cent, respectively. The original table contains data for nine other measurements which we have not included. Height has a coefficient just a trifle smaller than sitting height in their table, and these are definitely lower than any other physical measurements presented, although there are ten other measures of a linear character, i. e., either length or diameter. Weight shows the highest percentage of variability. Circumferences, in general, range about midway between these extremes. It is not necessary to consider each one of these measures separately. The technic of taking them has some bearing on the results. The point that needs to be stressed is that such physical measurements vary from each other in a characteristic manner. As adults, we are most alike in stature and least alike in weight.[3]

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2. Davenport, C. B., and Love, A. G.: Army Anthropology, Washington, D. C., Gov't. Printing Office, 1921, p. 234, table 103.

3. The reader may be inclined to criticize the use of army data in this connection, as height is a qualifying consideration in selecting soldiers. The extreme lower statures do not appear in their normal frequency in the data on army anthropology, but this fact does not destroy the fundamental nature of the comparison stressed in the foregoing. Harris and Benedict (A Biometric Study of Basal Metabolism in Man, Carnegie Inst. Wash. Pub. No. 279, Washington, 1919.) in table 9, on page 54, cite from various sources a large amount of data on stature for men and women. They give data for seventeen different groups of men—students, convicts, persons of various nationalities and others. The coefficients of variation range from 3.66 to 4.3 per cent and give an average of 3.88 per cent. From the literature they have compiled data on ten groups of women. Here the range of variation is from 3.7 to 4.4, and the average is 4.08 per cent for stature. The number of series of body-weight results available for comparison is decidedly more limited. No doubt can exist however, that weight is a much more variable character than is stature. No group of weight data that we have been able to find shows a variability as small as 10 per cent; in some groups it is as high as 25 per cent. Our own data on patients with diabetes (Root and Miles: Physical Measurements of Diabetic Patients, J. M. Research **2**:173, 1922) may be cited in this connection. For seventy-seven men with diabetes the average height was 171 cm., with a variability of 3.5 per cent; average weight, 61.2 Kg., with variability of 15.4 per cent. The fifty-six women with diabetes had an average height of 159 cm., with a variability of 2.9 per cent; the weight was 53.9 Kg., with a variation of 19.7 per cent.

It is the usual practice to measure a person's height as the easiest measurement to make, and on that basis to estimate what he should weigh. For this estimation a "height-weight table" is used which commonly takes into account no other factors than sex and age.[4] It seems to us a curious and an indefensible position to make that one particular linear measure in which we are most alike the basis, often the sole basis, for predicting the normal value for a factor which exhibits the most marked deviation even in an homogenous group of physically fit soldiers.

TABLE 1.—*"Army Anthropology" Data on 100,000 White Troops Showing the Coefficient of Variation for Different Physical Measurements*

Part Measured*	Average Observed Value	Standard Deviation	Coefficient of Variation, per Cent
Body weight (kilograms)	65.6	7.7	11.7†
Height	172.0	6.7	3.9
Sternal notch	141.2	5.9	4.2
Sitting height	90.4	3.5	3.9
Span	175.6	7.9	4.5
Shoulder width	41.8	2.4	5.8
Pelvic transverse diameter	29.4	2.8	9.7
Depth of chest	21.6	1.9	8.7
Transverse diameter of chest	29.0	2.4	8.3
Girth of chest	88.8	5.1	5.7
Girth of waist	77.9	6.0	7.7
Circumference of thigh	52.7	3.7	7.1

* All values are given in centimeters except body weight, which is in kilograms.

† As published (table 103, page 234), Davenport and Love give the coefficient of variation for weight as 3.587 per cent. This is a mistake without doubt for no such value is characteristic of weight measurements. Curiously, a similar mistake is made in their table 104 for colored troops. Harris and Benedict, page 58, refer to nine groups of weight data, not their own, and the coefficients range from 10.4 to 25.1 per cent. In their own group of data, their table 2, the coefficients of variations for weight range from 11.2 to 20.3 per cent.

CORRELATION OF BODY WEIGHT, HEIGHT AND CHEST CIRCUMFERENCE

If, in conformity with the old myth, man's shape were perfectly spherical, and if all men were equally dense, then the person with the greatest height or width, whichever we choose to call it, would weigh the most. There would be perfect correlation between stature and weight or waist diameter and weight, or circumference and weight, etc. It is, of course, a fact that as correlations go in biologic material, there is a high degree of positive correlation between height and weight, taking man as he is found. In 1899, Pearson pointed out that this correlation for English undergraduate students, expressed in figures, was + 0.49. In the data on army anthropology referred to in the foregoing, it was + 0.48. The many correlations between height and

4. The Life Extension Institute, Inc., New York, publishes (form 521), a table entitled "The Ideal Build" in which they make the statement that "gain in weight with advancing years, beyond age 35, is not physiologic." They recognize three main types of skeletal frame work: slender, medium and massive. The latter is allowed from 10 to 15 per cent increase over the values given in their table. The "slender" are allowed a reduction of 10 per cent.

weight that have been made in groups of children or persons well within the growth period are not pertinent to our discussion. There are, however, considerable data on adults that verify this rather high correlation. For example, the data of the Nutrition Laboratory, so carefully treated by Harris and Benedict [5] show the following correlations between height and weight: 136 men, $+ 0.57 \pm 0.04$; 103 women, $+ 0.33 \pm 0.06$. They found, furthermore, that when partial correlations were computed so as to eliminate the influence of age as a factor, the values of these constants were but slightly modified.

The fact that height and weight are positively correlated in a striking degree is, of course, significant, and may not be denied; but the presence of a positive correlation is no warrant in itself for making one factor the sole basis for predicting normalcy in the other. We are not spherical. Other measures than height must be taken into account, especially since we have found that these other linear measures (skeletal widths) vary more from person to person and so necessarily exercise a greater influence in determining what is essentially the cubic contents of the body. The desirability of introducing into the prediction basis for weight some factor in addition to height and age was urged long ago by Bornhardt, the Russian military surgeon. Recently Dreyer,[6] and particularly Gray,[7] have written on this question. Gray has performed important service in regard to the whole problem of weight prediction by his critical reviews of the earlier literature and by comparisons of results secured when predicting weight by different standards. In our article on the physical measurements of patients with diabetes,[8] we emphasized this point but showed that chest circumference recommended by some as the needed factor clearly was not appropriate. The correlation between the circumference of the chest and the weight is much higher than it is for stature and weight. These correlation values for girth of the chest and weight range from about $+ 0.65$ to $+ 0.95$. The circumference of the chest is an overall cross-sectional measure. It is a second power measure of that for which body weight is a third power measurement. Accordingly, they will correlate conspicuously, for we are measuring practically the same thing, in one case in centimeters and in the other in kilograms. The plump person having a large cross-sectional area on the basis of the circumference of his chest makes for

5. Harris, J. Arthur, and Benedict, Francis G.: A Biometric Study of Basal Metabolism in Man, Carnegie Inst., Wash. Pub. No. 279, Washington, 1919, p. 59, table 12.

6. Dreyer, G., and Hanson, G. F.: The Assessment of Physical Fitness, London 1920; reprinted by Hoeber, New York, 1921.

7. Gray, H., and Mayall, J. F.: Body Weight in Two Hundred and Twenty-Nine Adults. Which Standard is Best? Arch. Int. Med. **26**:133, 1920; Gray, H., and Root, H. F.: Weight Prediction by the Formulae of Bornhardt, of Von Pirquet, and of Dreyer, Boston M. & S. J. **185**:28, 1921.

8. Root, H. F., and Miles, W. R.: Physical Measurements of Diabetic Patients, J. M. Research **2**:173, 1922.

himself an "ample" standard, and we "predict as normal" nearly that which we find him to be in weight.[9] Surely this is absurd and dangerous, as it befogs the whole question.

What is much needed at present is a clearer understanding of the relationship between the physical measurements that may be practically taken on an adult man or woman, and the marked fluctuations in the body weight of adult persons. What measures, consistently and pronouncedly, reflect gain or loss of weight independent of the factor of growth? What measures show a high degree of stability in the face of such changes in weight in the adult? It seems to us that only on the ground of such information can progress be made. Unfortunately, with all the measuring that has been done on living man, little concerns itself with this question. Before presenting the data which we have collected on a small group of adults with hyperthyroidism in whom rapid weight changes followed operation, certain other related material should be reviewed.

CHANGES IN BODY MEASUREMENTS DURING SEVERE UNDERNUTRITION

In 1915, Benedict [10] published his important study of prolonged fasting. This investigation was conducted at the Nutrition Laboratory in Boston from April 10 to May 14, 1912. The subject of the thirty-one-day fast was Mr. A. Levanzin of Malta, a man 40 years old. He was close to average weight for his height, judged by the Medico-Actuarial Standards of 1918. Dr. H. W. Goodall, the physician who repeatedly made physical examinations of Levanzin during the fast, had this to say as a summary on the patient's physical condition:

"The general appearance of the subject remained good throughout the period of observation. A gradual loss of body tissue was evident, but the changes were not marked from day to day. The most pronounced change was in the abdomen, which became flat as soon as he ceased to take food and was distinctly retracted after the fifth fasting day. This for the most part appeared to be due to the prompt disappearance of gas in the intestines. The actual loss in body tissue appeared to be quite evenly distributed over the body, but was most noticeable in the tissue of the back of the neck, in the sinking in of the supra- and infraclavicular spaces, and in the prominence of the ribs. The muscles of the extremities, which were moderately firm at the beginning of the fast, appeared to have softened to a slight degree. . . ."

An elaborate series of anthropometric measurements was made on Levanzin under the direction of Dr. W. L. Anderson of Yale. This series included mostly measurements of girth. Such measurements of breadth as were used were not started until the twelfth day of the fast.

9. Gray and his collaborators, Mayall and Root, found that the Bornhardt and the Dreyer Methods, which advocate the use of chest circumference, give prediction results closer to actually observed weights than do other methods.

10. Benedict, Francis G.: A Study of Prolonged Fasting, Carnegie Inst. Wash. Pub. No. 203, Washington, 1915.

Table 2 is compiled from data given by Benedict (see his page 68) and our own computations of these data. Values are given for various physical measurements taken on Levanzin just prior to the fast and again on the thirty-first day of the fast.[11] The percentage of loss is computed on the basis of the preliminary value in each case. He lost 21.8 per cent of his original weight, but there was no change in height. The depth of the abdomen decreased 19.1 per cent (see Goodall's statement), but there was much less change in the depth of the chest. None of the measurements for girth or circumference show losses equal to the loss in weight, but some of them are not much less: waist, 19.6; thigh, 18.7 per cent. The Levanzin fasting data illustrate strikingly that circumferences as usually measured depend on present weight condition. Measurements of the bony width unfortunately were not made.

TABLE 2.—*Physical Measurements at the Beginning and End of a Thirty-one Day Fast; Subject, Levanzin*

Name of Measurement	Just Prior to Fast	On 31st Day of Fast	Percentage Loss
Body weight	60.6	47.4	21.8
Height	170.7	170.7	0.0
Girth of waist	78.0	62.7	19.6
Chest girth (normal)	87.9	80.0	9.0
Circumference of thigh	48.8	39.6	18.7
Right biceps, flexed	27.9	23.9	14.3
Right forearm, extended	25.4	22.4	11.8
Right calf	33.5	30.0	10.4
Left calf	34.5	29.5	14.5
Depth of chest	25.4	22.9	9.8
Depth of abdomen	18.8	15.2	19.1

Another publication which has been issued by the Nutrition Laboratory gives the data on two groups of twelve men each whose diet was so restricted as to produce considerable change in body weight.[12] The twelve physically fit young men who made up Squad A lived for approximately four months on an energy intake of about 1,900 calories a day each, and thereby lost an average of 10.7 per cent in weight. The associated average changes in different circumferences were the following: axilla, 9; umbilicus, 6.9; nipples, 5.7; hips and buttocks, 4.6; and thigh, 8.3 per cent. The correlation between the percentage losses in weight and in girth at the umbilicus was 0.76 ± 0.082. Squad B was constituted of twelve men who took a more severe reduction in diet for a shorter period. As a result they lost, on the average 6.5 per cent of their former weight. The associated losses in girth were: axilla, 6.1; umbilicus, 5.1; nipples, 4.3; hips and buttocks, 4; and circumference of

11. The subject took absolutely no food during the thirty-one day period. The distilled water consumed each day varied from 720 to 900 cc. He even bathed in distilled water.

12. Benedict; Miles; Roth, and Smith: Human Vitality and Efficiency Under Prolonged Restricted Diet, Carnegie Inst. Wash. Pub. No. 280, Washington, 1919, p. 239, table 17.

thigh, 6.6 per cent. This last is noteworthy in being as great as for weight. All of these data from this "low-diet research" were made in connection with the taking of the DuBois measurements for determining body surface. They demonstrate the weight-circumference relationship stressed in the foregoing.

The largest and at the same time scientifically accurate mass of observations on physical modifications under inanition were reported on in 1923 by Professor Ivanovsky.[13] The report, which is edited by Dr. A. Hrdlicka, is based on the changes caused by famine in Russia. Observations by anthropologists were continued for three years at semi-annual intervals so that all subjects were measured six times. Presumably the data given represent the first and sixth measurements. The report is based on 1,248 men, their ages ranging from 25 to 55 years, and 830 women, whose ages ranged from 20 to 55 years. The subjects belonged to several different ethnic groups. There is scant indication of the manner or conditions of the measurements or of the extent of the reduction in food. The data published cover the following points:

1. Loss in weight in percentage groups—1-10, 11-20, 21-30, and 31-40.
2. Stature.
3. Thoracic circumference in percentage of stature.
4. Trunk length, jugular incisura to public symphysis, (with men only).
5. Length of arm in percentage of stature.
6. Length of leg in percentage of stature.
7. Length of head, vertex to chin.
8. Horizontal circumference of head.
9. Anteroposterior diameter of head.
10. Transverse diameter of head.

We have computed the losses for the different physical measures and give these percentages for men and women separately in table 3. It is not possible for us to secure from the Ivanovsky article a satisfactory value as a mean for loss in weight. He gives this only in terms of the percentage of persons falling within certain ranges of loss in weight. Probably the average reduction in weight was 15 or 16 per cent. Among those examined, every person decreased in weight, and this decrease was the noteworthy change as a result of the famine. The decrease was rapid within the first month, and weight reached its lowest point in the third or rarely the fourth half year of the famine. There were only slight changes in weight later, even though the amount of food was somewhat increased. The percentage decrease for obese persons was greater than for thin people, and in general, the decrease was more rapid and reached its lowest point more quickly in women than in men. Ivanovsky describes weight in man as the character which shows "most frequent and greatest variation," and he states that it is more variable

13. Ivanovsky, Alexis: Physical Modifications of the Population of Russia Under Famine, (Translated by W. Jochelson and edited by A. Hrdlicka) Am. J. Phys. Anthrop. **6**:331, 1923.

among civilized people than among uncultured tribes. The table shows slight losses, less than 1 per cent, in length of the arm and leg. The decrease in stature is unprecedented. A shrinkage of 46 mm. for the men and 39 mm. for the women seems remarkable, especially when we refer to the Levanzin data. Ivanovsky does not appear to be much surprised at the change in stature. He notes that army recruits have reduced the stature temporarily from 30 to 50 mm. by standing, walking and bearing heavy burdens. The thoracic circumference was reduced 7.2 per cent for men. This was about the same ratio to the change in weight as occurred in Levanzin. The diameters of the head, even though practically bony measures, give definite decreases. A change of 4 per cent in the transverse diameter means a reduction of 6 mm. for

TABLE 3.—*The Ivanovsky Data for the Influence of Famine on Physical Measurements of Men and Women in Russia*

Name of Measurement	Men, Percentage of Loss	Women, Percentage of Loss
1. Weight	15.9*	15.2*
2. Stature	2.8	2.5
3. Thoracic circumference	7.2	...†
4. Length of trunk	6.2	...†
5. Length of arm	0.7	0.3
6. Length of leg	0.6	0.0
7. Length of head	4.1	4.3
8. Circumference of head	3.7	3.4
9. Head diameter, anteroposterior	2.2	1.7
10. Head diameter, transverse	3.9	4.0
Weight:‡		
1 to 10	28	32
11 to 20	49	50
21 to 30	21	18
31 to 40	1	0

* An approximation from the data as published.
† No data are given for the women.
‡ Different ranges for percentage of loss of weight; for example, 49 per cent of the men lost from 11 to 20 per cent in body weight.

both men and women. We can but regret that it was not practicable to make any pelvic or other body width measurements. These data show, in general, that weight is the least stable measure; thoracic circumference is next, and length, particularly of the extremities, is the most stable. Even bony measurements change appreciably under a long period of famine.

BODY MEASUREMENTS DURING RAPID GAIN IN WEIGHT AFTER THYROIDECTOMY

Our own data concern gains in weight shown by adults following operative treatment of hyperthyroidism. These measurements were made in the thyroid clinic at the New England Deaconess Hospital in Boston by permission of Dr. F. H. Lahey. No selection was exercised except that the patients all had had high basal metabolic rates before operation. The patients were measured carefully by one of us (H. F. R.) a day or so before operation and also when tests for

metabolism were made. About six months following thyroidectomy, they were again measured in the same manner and by the same person. The two sets of measurements are directly comparable.

(*a*) *Methods.*—The particular group of physical measurements employed did not concentrate on circumferences as is ordinarily done, but placed more stress on body widths. Each measurement was chosen with the following considerations in mind: (1) practical applicability for both men and women; (2) its recognition as a standard measure familiar to physical anthropometry; (3) the relative accuracy with which the measure could be taken promptly, and (4) skeletal measurements in which the calipers when applied would be against bony resistance. The measurements and procedures in most instances followed the recommendations of Hrdlicka.[14] Each patient wore a hospital nightgown, the weight of which was deducted, so that the results given for body weight are net and represent the weight taken during a fasting condition.

Height was taken with the subject standing erect, with heels, buttocks, shoulders and head applied against a vertical wall to which the centimeter scale was attached. The visual axis was horizontal. With the subject standing in the same position, the height to the suprasternal notch was measured by projection with the use of a level and a plumb bob (Hrdlicka, pages 66-67). The stem length, ordinarily termed "sitting height," was taken after the manner of Dreyer[15] with the subject seated on a level floor, the knees flexed, special care having been taken that the sacral region was well applied to the vertical. Taken in this manner, the measurement is freer from interference by the voluntary contraction and the thickness of the gluteal muscles. The three measures of length—stature, sternal notch and stem length—were taken by using the simple double meter-stick and triangle device which we have described elsewhere.[16] The span of the olecranon, total distance from tip to tip of elbows, forearms flexed, has been used little if at all by anthropometrists. It has the practical advantage of bony terminals, and when thus flexed, the subject cannot voluntarily modify the shoulder girdle to the same extent through stretching that he can in the ordinary span measurement. The span of the olecranon was taken with the subject flat against the wall with one elbow applied to the adjoining wall.

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14. Hrdlicka, A.: Anthropometry, The Wistar Institute of Anatomy and Biology, Philadelphia, 1920.

15. Dreyer, G., and Hanson, G. F.: The Assessment of Physical Fitness, London, 1920, p. 5.

16. Miles, W. R., and Root, H. F.: A Simplified and Trustworthy Means of Measuring Stature, Boston M. & S. J. **192**:111-112, 1925.

In measuring diameters of body width, we did not use the straight arm sliding caliper ordinarily employed in anthropometry, but rather the large curved caliper of the obstetrician. This had rounded points which can be pressed well in against bony resistance, and which can be read at the moment. The acromion measure for shoulder breadth was the caliper distance between the superior external borders of the acromion processes. The pelvic transverse diameter used was the maximal distance between the external margins of the iliac crests. The depth of the chest was taken as the horizontal distance from the lower end of the sternum to the posterior vertebral process of the corresponding level. The diameter of the bony transverse chest was measured at the level of the xiphoid process. Girth of the chest was measured at the level of the nipples and was the median of the subject's natural inspiration and expiration girths. Such a series of measurements is not difficult to take and requires not more than ten or fifteen minutes when the subject is ready.

(*b*) *Results.*—Data for fourteen patients, eleven women and three men, are summarized in table 4. The range in age was from 23 to 61 years. Many other patients were given the preliminary measurements, but it was not possible to secure the second set. We are aware that the group is small, but, considering the extreme paucity of data on this general problem, our observations perhaps have an interest out of proportion to the size of the group examined. Ordinarily it is not good practice to include women and men in the same physical average, but careful scrutiny of the results fails to reveal any injustice from considering them all as one group. The presentation in table 4 is fairly self explanatory: weight is given in terms of kilograms, while the other physicial measures are given in centimeters. The mean preliminary weight was 53.3 as compared to 62.4 kilograms approximately six months after treatment. Every patient showed an increase in weight. The increases ranged from 4 to 14, averaging 9.1 kilograms, which represents a change of 17.1 per cent with the earlier weight as the base. The period between the two series of measurements as stated in the table was approximately six months; actually, it averages one hundred and ninety-five days. The shortest interval which elapsed between the two series of measurements was one hundred and sixteen days; the subject was a woman. During this period she gained 7.7 kilograms, or 14.7 per cent. The longest time which elapsed between series was two hundred and ninety-three days; this subject, a woman, gained 7.9 kilograms, an increase of 13.2 per cent. The extreme gains in weight were those of a man showing 26.1 per cent (13.7 kilograms) and of a

woman with a gain of 25 per cent, an increase in weight of 11.9 kilograms. The smallest gain was that of a woman, who in an interval of one hundred and ninety-four days gained 4.4 kilograms, equaling 9.3 per cent. The percentage of the loss in body weight for this hyperthyroid group is about the same as the loss for the Russian group and not quite so large as the loss in the case of the thirty-one day fast.

The results for body length in general indicate but slight change. Height increased 0.1 per cent, sternal notch height 0.2 per cent and stem length 0.4. In all three of these measures there were subjects who did not show a gain but rather a slight loss. The losses were always less than 1 cm., and the gains were usually less than 1.5 cm.[17]

TABLE 4.—*Physical Measurements in Patients with Hyperthyroidism Before and After Operation*

Part Measured*	Average Observed Values		Direction and Amount of Change Exhibited				
	Just Prior to Operation	Six Months After Operation	Number of Cases: Plus	Number of Cases: Minus	Range of Difference	Average Difference	Per Cent Difference
Body weight	53.3	62.4	14+	....	+14 to +4	+9.1	+17.1
Height	162.8	162.9	9+	5—	+1.5 to —0.8	+0.1	+ 0.1
Sternal notch	132.6	132.9	10+	3—†	+1.1 to —0.4	+0.3	+ 0.2
Stem length‡	85.7	86.0	8+	6—	+2.2 to —0.9	+0.3	+ 0.4
Span, olecranon	86.1	86.0	5+	8—†	+1.6 to —2.0	—0.1	— 0.1
Shoulders, acromion	34.2	35.0	10+	4—	+3.0 to —0.7	+0.8	+ 2.3
Iliac, maximal diameter	29.3	29.4	9+	5—	+0.4 to —0.3	+0.1	+ 0.5
Depth of chest	18.8	19.6	11+	3—	+2.0 to —0.3	+0.8	+ 4.2
Transverse diameter of chest	23.9	24.6	10+	4—	+2.7 to —0.5	+0.7	+ 2.7
Girth of chest	73.3	79.7	14+	....	+21 to +1.0	+6.4	+ 8.8
Basal metabolism, calories per Kg.	38.2	23.9	....	14—	—5 to — 23	—14.3	—37.1

* All in centimeters except that body weight is in kilograms.
† Measurement missing in one subject.
‡ Taken in the manner prescribed by Dreyer.

The span of the olecranon was the only one of our anthropometric measurements that gave an average decrease, and this was slight, being only 0.1 per cent. Eight patients, however, showed decreases and five increases; the range was from + 1.6 to — 2.0 cm. The change probably came through a shift in the position of the shoulder blades.

There were four standard measures for body width. There was an average increase of 2.3 per cent in shoulder breadth, which in terms of the measurement is 8 mm. Shoulder width increased in ten of the subjects, in one as much as 30 mm., i. e., 7.5 per cent. This man had gained 19.9 kilograms. Decreases in shoulder width were slight; in two sub-

17. One patient showed a gain of 2.2 cm. in stem length. This is so far out of line with the plus values given by other subjects for the stem length that it seems probable that the base of the spine was not pressed back against the vertical in the preoperation measurement.

jects this width decreased 2 mm. in each, in two others, 5 and 7 mm. The average iliac diameter before operation was 29.3 and after treatment, 29.4 cm. This diameter increased in nine subjects and decreased in five, but the total range covered was only 7 mm. eleven women show a measurement range of 272 to 328 mm. in the iliac diameters following treatment. The latter figure is the measurement found for the heaviest member of the group, 66.8 kilograms. A woman with an iliac diameter of 277 was the lightest, 54.8 kilograms. The one in whom this diameter was 272 had a postoperation weight of 57.7 kilograms, but she was not the shortest of the women. On an average, the change in weight occasioned a shift of only 0.5 per cent in the iliac diameter. The depth of the chest shows a somewhat larger percentage of increase than does the transverse diameter of the chest, 4.2 as against 2.7 per cent. A definite majority of the patients showed an increase in each measurement. The range of increase was larger for the transverse diameter. In millimeters, the average change was almost the same for both diameters of the chest.

Increase in the girth of the chest taken at the level of the nipples was the invariable result when the weight had increased. This definite change in the circumference was from 1 to 21 cm.; on the average it was 6.4 cm., which amounts to 8.8 per cent. This value compares fairly well with the 7.2 per cent found for Russian men and also with the 9 per cent found for the fasting man. Judging from the data on Levanzin (table 2) and that accumulated on Squads A and B in the low diet experiments, the girth at the level of the nipples is not as much disturbed by loss in weight as is the circumference at the axilla or at the umbilicus. Nevertheless, this measure is in a class by itself so far as amount of change is concerned when compared with body length or diameters.

Circumferences, in general, reveal more definitely the build of the body than does stature, as Davenport urges in his monograph on body-build and its inheritance.[18] The circumferences reflect also the present weight status or nutritional condition of the person in a marked degree. The native and more inherent body-build characteristics, as seen from the data presented, are revealed in the skeletal widths, which can be so taken as to escape in large part interference from any present overweight or underweight condition.

CONCLUSIONS

The group of data presented in this paper mutually supplement each other and lead to the following statements.

18. Davenport, C. B.: Body-Build and Its Inheritance, Carnegie, Inst. of Wash. Pub. No. 329, Washington, 1923.

1. Body weight in adults is normally the measure showing the largest variability, while stature is the least variable of the ordinary physical measurements. Stature is, therefore, not the best basis from which to estimate normal weight.

2. In adults who have shown marked changes in weight through fasting or decreased intake or as a result of thyroidectomy (new data), changes in circumferences and girths parallel closely changes in weight, and hence are ruled out as a basis for weight prediction.

3. Certain bony body widths, which have a natural variability about midway between stature and body weight, are found to change but little when persons lose or gain as much as from 15 to 20 per cent in weight. These width diameters, notably the intercrestal iliac diameter, are important in determining body-build and should receive due emphasis in tables on normal weight.

ANTITHROMBIN TEST IN TYPHOID FEVER

IMPROVEMENTS IN TECHNIC *

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Kitzmiller and I have certain new developments in technic to offer those who may be interested in our antithrombin test previously described.[1] These are, first, the use of purified fibrinogen and thrombin solutions instead of citrated horse plasma and serum; second, the adaptation of the method to from 0.1 to 0.2 cc. of the patient's serum so that venipuncture may be dispensed with; and, third, such simplification of the method that laboratory technicians anywhere may perform it, without possessing special knowledge of blood clotting.

The first alteration in technic, the use of purified fibrinogen and thrombin solutions, was prompted by the discovery that repeated bleedings of an animal to obtain the citrated plasma needed caused the development of such an excess of antithrombin in the animal's blood as to render it an unfit medium for detecting an excess of this element in a patient's blood. By the use of the purified thrombin and fibrinogen solutions described below, almost all the antithrombin of the horse plasma is eliminated, and in this way one of the most troublesome variables of the method is avoided. The second change, the use of 0.1 or 0.2 cc. of the patient's serum, is of particular value in China, where venipuncture is dreaded by the people, but a finger prick is accepted stoically at any time. By using the bent Wright tubes of about 0.5 cc. capacity, one may easily obtain sufficient blood from the patient's finger or ear. The use of serum instead of citrated plasma allows the choice of this method of drawing the blood. The third improvement consists in the taking of only a single reading of the thrombin activity of the mixtures at the end of two hours, instead of the repeated readings previously advised. This is made possible by the use of the purified solutions and the elimination of the antithrombin variable of the citrated test plasma.

PREPARATION OF SOLUTIONS

The following solutions are prepared and kept on ice:

1. *Blood Fibrinogen.*—Blood of any mammal (we use the horse) is drawn into a vessel containing sufficient sodium citrate to give a final concentration of 0.5 per cent, the blood being well stirred to provide prompt mixing. The plasma is collected by centrifugalization. To 25 cc. of plasma are added 4 Gm. sodium chloride. The precipitated fibrinogen is collected and washed several times in

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1. Mills, C. A., and Kitzmiller, K. V.: Aid in the Diagnosis of Thyroid Fever: A New Laboratory Method, Arch. Int. Med. **38**:544 (Oct.) 1926.

15 per cent sodium chloride solution containing 0.5 per cent sodium citrate. It is finally dissolved in 25 cc. of 0.5 per cent sodium citrate solution, and in this form will keep several days in the icebox.

2. *Thrombin.*—To the 25 cc. of plasma from which the fibrinogen has been removed in the foregoing, as described, 9 Gm. of ammonium sulphate are added, and the precipitate collected on a filter. It is allowed to drain thoroughly on the filter and finally all sulphate solution possible is pressed out between layers of filter paper. This obviates the necessity of dialyzing out the ammonium sulphate. This precipitate contains practically all the prothrombin of the plasma. It may be bottled as the moist paste, and in this form it will keep for weeks. When desired for use, 0.25 Gm. is dissolved in 10 cc. of water, and to this solution are added 2 cc. of a 0.1 per cent emulsion of cephalin and 2 cc. of 1 per cent calcium chloride solution. After this mixture is allowed to stand at room temperature for thirty minutes to get a maximum thrombin production, it is ready for use. It will then hold practically a constant thrombin activity for several hours, but should not be used on a succeeding day.

METHOD OF TEST

The actual procedure of the test now is as follows: Blood is obtained by a finger prick, drawn into a Wright tube, allowed to clot and the serum squeezed out, or the clot is broken up and centrifugalized down. The serum is drawn off through a capillary pipet, and 0.1 or 0.2 cc. is measured into a small test tube and heated in a water bath to 60 C. for ten minutes. Five or six serums may be tested in one series just as easily as a single specimen. Along with the patients' serums a similar procedure must always be performed on the fresh serum of a healthy person. (I use my own blood drawn in the fashion described in the foregoing.) The heated serums are now cooled, and to each tube is added three times as much thrombin solution as there was serum originally taken. If 0.1 cc. serum is taken, then 0.3 cc. thrombin solution is added to that tube. In addition, one tube of 0.9 per cent sodium chloride solution as a control is prepared in a similar fashion. The thrombin solution here used should be prepared as directed in the foregoing at least thirty minutes before it is to be used.

This series of tubes is set aside at room temperature for two hours, and at the end of this time, 0.2 cc. of each mixture is added to 0.25 cc. of the fibrinogen solution in a water bath at from 38 to 40 C., and the time required for clotting of the fibrinogen is noted. The saline control will probably clot the fibrinogen in about thirty seconds, the control serum tube in from four to six minutes, and any typhoid serum tube in double the time required by the control serum. The tubes should not be shaken, but should be inclined gently to note clot formation.

Precautions in handling typhoid serum to prevent infection in the technicians is necessary only up to the time of heating the serum, as the heating to 60 C. for ten minutes minimizes the risk. Kitzmiller and I, however, always insist that laboratory technicians and assistants who handle the blood of patients should be given the regular course of typhoid vaccine.

When we have reduced the antithrombin method to a more satisfactory and exact form, we hope to submit some interesting data as to its significance in the near future. Typhoid fever is prevalent at all times in Peking. Our work here so far has drawn a sharp line of distinction between typhus and typhoid, the former never exhibiting a considerable increase in antithrombin. This point is of great value, since the two fevers are so similar during the early part of their course, when both Weil-Felix and Widal reactions are negative.

PRESENT STATUS OF CURABILITY OF BRONCHIAL ASTHMA

WITH REPLIES TO A QUESTIONNAIRE *

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Reports of the benefit derived from the methods of treatment of bronchial asthma are extremely diverse and often depend on the enthusiastic preconceptions of the physician, the psychic susceptibilities of the patient and the spontaneous tendency of the disease to remissions, aggravations and improvement.

In the earlier work on anaphylaxis and protein sensitization, the parallel symptoms suggested asthma to be a phenomenon of anaphylaxis.[1] According to this view, a person who has asthma is sensitized to a definite substance, and an attack occurs every time this substance enters the circulation. In the actual processes which take place in nature, the effective doses may be infinitely small; and it may well be possible that the minute quantities contained in the emanations from horses, cats or guinea-pigs are sufficient to act as a toxic dose and cause the nonfatal stenosis of the bronchi evidently present in an asthmatic attack in man. Perhaps certain digestion products of the proteins now and then become absorbed into the circulation from the alimentary canal, in some cases in an abnormal stage. The following parallel facts may be recalled: (1) the sensitization to anaphylaxis may be hereditary or acquired; (2) anaphylaxis is specific; (3) animals sensitized to a definite protein can be intoxicated only by that protein, and (4) atropine which relieved asthma, relieved also the anaphylactic attack, as discovered by Auer and Lewis.[2]

Sensitization tests have been held to indicate protein intoxication. The first sensitizing dose of egg white injected into an animal is digested, but the process goes on so slowly that no effect can be seen. An immediate effect on reinjection, especially a fatal issue, depends on the rapidity with which the protein is split up and its poisonous constituent set free.[3]

Manwaring believes that increased specific capillary permeability will ultimately be shown to be the dominant fundamental physiologic change

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1. Meltzer: Bronchial Asthma as a Phenomenon of Anaphylaxis, J. A. M. A. **55**:1022 (Sept. 17) 1910.

2. Auer and Lewis: J. Exper. Med. **12**:151, 1910.

3. Vaughan: Am. J. Med. Sc. **145**:161 (Feb.) 1913.

in protein sensitization, to which all other anaphylactic reactions are secondary.[4]

The brilliant work of Weil is most significant as having shown that the anaphylactic reaction is cellular.[5] Immune bodies in the blood do not contribute in the slightest degree to its production.

Experimental anaphylaxis, on the one hand, and such diseases as asthma, hay-fever and urticaria, on the other have another feature in common. They are all associated with an eosinophilia. Moschcowitz considered the invasion of eosinophils in increased numbers into the organism as the expression of an active agent or the agent itself in the production of anaphylaxis.[6] This is further emphasized by the fact that through continued parenteral administration of foreign protein, a peripheral blood eosinophilia may be produced in animals. Following recovery from anaphylactic shock, an intense eosinophilia likewise occurs, and the lung tissue exhibits a marked eosinophilic infiltration, with a peribronchial collection of these cells. Similar changes may be produced by inhalation of serum in animals sensitized intraperitoneally. In Arthur's skin phenomenon, the cells of the inflammatory swellings are chiefly eosinophils. A local eosinophilia of the submucosa is seen in the gut of dogs following anaphylactic enteritis. It is possible that certain products are formed in parenteral administration of protein which exert a positive chemotactic action on eosinophils; they are attracted from the blood and bone marrow in which they are present in increased numbers.[7]

As shown by the data in this article, as well as by the work of a number of authors, anaphylaxis may be dismissed from consideration in this disease. Anaphylaxis is an induced hypersensitiveness caused by the presence of specific antibodies in certain tissues. The symptoms of anaphylaxis are caused by the meeting of these antibodies with the respective antigen in those tissues. It has been shown to be non-inheritable in the biologic sense. It seems necessary to conclude, first, that if anaphylaxis does occur in man, it does so rarely, and second, that there is not any positive evidence that anaphylaxis occurs in human beings.[8]

Concerning hay-fever, Cooke indirectly suggests that it may be a manifestation of an idiosyncrasy to ragweed similiar to the idiosyncrasy to drugs such as quinine and acetylsalicylic acid, and that it may not have anything to do with anaphylaxis.[9] Again, it seems hardly correct to class hay-fever or asthma with the typical anaphylaxis seen in the

4. Manwaring: Capillary Permeability in Anaphylaxis, J. A. M. A. **80**:303 (Feb. 3) 1923.
5. Weil: J. M. Research **30**:87, 1914.
6. Moschcowitz, Eli: New York M. J. **93**:15, 1911.
7. Schlecht and Schwenker: Deutsche Arch. f. klin. Med. **108**:405, 1912.
8. Coca: J. Immunol. **5**:363 (July) 1920.
9. Cooke: Allergy in Drug Idiosyncrasy, J. A. M. A. **73**:759 (Sept. 6) 1919.

artificial sensitization of animals and man, because the principles of anti-anaphylaxis do not apply. Thus, active sensitization of guinea-pigs to ragweed pollen extract apparently is impossible.[10] Attempts to transfer antibodies from man to animals as well as the demonstration of circulating antibodies to ragweed in a test tube is at best variable. In active anaphylaxis the presence of circulating antibodies is one of the striking features, whereas in ragweed hay-fever, the presence of circulating antibodies is vague and doubtful.[11] Koessler[12] and Clowes[13] found that circulating antibodies decrease rather than increase as the process of immunity progresses. Yet the treatment with pollen substances for the purpose of immunization is still used, and an attempt is not made to arrive at a more basic cause for the asthma.

HEMOCLASIC REACTION AND VAGOTONIA

The path of study opens again into wider channels with the studies of Widal and his co-workers.[14] They attribute anaphylactic reactions and idiosyncrasy to a constitutional predisposition in which the person reacts with flocculation of the colloids in the blood serum, the so-called hemoclasic or colloidoclasic reaction. As part of this reaction, there is a sudden fall in the total number of leukocytes in the circulating blood. Thus in one patient, exposure to pollens, antipyrine or acetylsalicylic acid induced immediate hemoclasis, with a drop in the leukocytes, generalized eruption, sneezing and an attack of asthma. Chilling of the skin on stepping out of a warm bath was enough to bring on all the symptoms. This suggests that while anaphylaxis may be the cause of some of the manifestations, others must be ascribed to an idiosyncrasy, which proves that the underlying cause of both is the instability of the colloidal balance in the plasma.

That asthma is a manifestation of overexcitability of the pneumogastric system, has long been surmised.[15]

It is obvious that there is not a single cause, but that several factors, internal and external, combine in varying proportions in the clinical picture. Vagotonia is an indispensable element, but inadequate alone to induce asthma. Colloidoclasis is probably an effect, not a cause. These two elements recall the neurosis and the dyscrasia of the old school. Thus our predecessors, with clinical observation alone, recognized the main elements of the problem. The final solution must be sought in

10. Cooke, Flood and Coca: J. Immunol. **2**:217 (Feb.) 1917.
11. Besredka in Krauss u. Levaditi Handb. etc. Ergänzungsb., I., p. 246.
12. Koessler in Forchheimer Therapeusis of Internal Diseases, ed. 5, New York, D. Appleton & Co., 1914, p. 671.
13. Clowes: Proc. Soc. Exper. Biol. & Med. **10**:69, 1913.
14. Widal, Abrami and Lermoyez: Presse méd. **30**:189 (March 4) 1922.
15. Eppinger and Hess: Vagotonia, Nerv. & Ment. Dis., Monograph Series, New York, 1917.

biology and probably in physical chemistry, and, most important, in the phenomena of heredity.[16]

IMMUNITY AND DESENSITIZATION

The reports in the literature of spontaneous immunity in cases of protein sensitiveness are not a pledge for permanence of immunity. Thus Schloss studied eight infants affected with idiosyncrasy to egg.[17] The patients developed urticaria from one to three hours after the egg was ingested. Desensitization always occurred after the development of toxic symptoms and lasted for a period of from thirty-three to forty-five days. During this time, egg white could be ingested without harmful effect, and the cutaneous test to egg protein was negative. The cutaneous test to egg protein and the development of toxic symptoms after the ingestion of egg white were in close accord.

Contradictory opinions are entertained regarding the amount of antigen to be used in therapeutic prophylaxis. Sewall, from carefully conducted experiments on guinea-pigs, emphasized that small instillations of serum have a positive inhibiting effect over the development of anaphylaxis, but that hypersensitiveness is maintained by repeated application of the larger dosage.[18] He concludes that clinically better results may be expected by choosing a dosage of antigen which fails to produce an obvious reaction than by one which entails a marked disorder. After the use of vaccines clinically in a series of cases, Rackemann, on the contrary, concluded that good results occurred only in those cases in which the various doses of the vaccine are followed by local reactions at the site of inoculation.[19]

The confusion which exists is further indicated by Vaughan who states:

> If we may assume, from our meager knowledge of the immunology of this disease, that relief of symptoms following preventive inoculation is due to an increased tolerance (as in morphinism) rather than a true immunization; and that the condition resulting is one of so-called antianaphylaxis, the daily administration of small amounts would appear to be a more logical procedure than the giving of larger amounts at much longer intervals.[20]

The use of nonspecific proteins is exploited on the basis of beneficial clinical results. A nonspecific element enters largely into the benefits derived from specific desensitization. Milk has been used as a non-

16. Segard: Rev. de méd. **38**:457 (Sept.-Oct.) 1921.

17. Schloss: Desensitization in Cases of Food Idiosyncrasy, J. A. M. A. **73**:785 (Sept. 6) 1919; Proc. Am. Soc. for Clin. Investigation, 1919.

18. Sewall: J. Lab. & Clin. Med. **2**:874 (Sept.) 1917.

19. Rackemann: J. Immunol. **8**:295 (July) 1923.

20. Vaughan: Specific Treatment of Hay-Fever During the Attack, J. A. M. A. **80**:245 (Jan. 27) 1923.

specific agent of choice because of its ready supply and ease of production.[21]

It is evident that attempts at immunization have proved disappointing. The use of vaccines in this disease is entirely empiric, and their administration is not even in accord with the principles of vaccine therapy. Thus Rackemann and Thomas have the impression that prolonged use of vaccine appears to prevent relapses.[22] Such an observation is beset with fallacies in a disease so changeful as bronchial asthma.[23]

The need of apology for the use of vaccines in asthma is avowed in the following statement: "Although good proof of a cure brought about by vaccine is lacking, vaccines do good in many cases, and at least until we know more of the fundamental pathologic physiology of asthma, their use is reasonably justifiable." [19]

Again, Davidson asserts that complete desensitization in man cannot be obtained. The phenomenon of lessened sensitiveness produced by injections of protein extracts in cases of hypersensitiveness has been called hyposensitization. Most patients are obliged to take treatment every year, as the hyposensitization is temporary. In a few cases, it has been known to last three years after one series of injections.[24]

In a group of ninety patients treated with autogenous vaccine by Hutcheson and Budd, the longest duration of complete relief was three years.[25]

In five cases of Lord's series, there was complete freedom lasting from one to five years, with recurrence after this interval.[23] This may be due to avoidance of exciting causes or to spontaneous remission.

Making the necessary allowance, the following is perhaps in accord with more general experience in vaccine treatment: "Of the entire series of 131 patients, 7 per cent have been cured, 22 per cent have been definitely benefited, 10 per cent have been helped somewhat, 18.5 per cent have been relieved temporarily but 41 per cent have not been relieved at all." [19]

In one article, contradictory conclusions are expressed together with a mature skepticism:

> In a certain relatively small number of cases, especially in children, the tests are of greatest value in demonstrating the cause of symptoms, and in most of these cases treatment, by avoiding the corresponding food, gives remarkable results. Subsequent study showed moreover, that in only about 13 of 100 cases was the finding of the test to food or animal protein really important and of use in further treatment. This figure is very small, but, as

21. Schiff: Am. J. M. Sc. **166**:664 (Nov.) 1923.

22. Thomas: Treatment of Asthma with Autogenous Vaccines, Arch. Int. Med. **34**:79 (July) 1924.

23. Lord: Diseases of the Bronchi, Lungs and Pleura, Philadelphia, Lea & Febiger, 1925.

24. Davidson: J. S. Carolina M. A. **19**:377 (Jan.) 1923.

25. Hutcheson and Budd: Virginia M. Monthly **46**:218 (Feb.) 1920.

a matter of fact, the ability to really help a small number of patients undoubtedly justifies the great amount of routine work on many patients. Emphasis should be placed on the necessity of a fairly gross interpretation of any positive test. Too delicate or fine a reading merely clouds the picture and in addition renders further progress in this already obscure branch of science even more difficult.[26]

This profusion of articles has added voluminously to the literature on the subject, advancing the science of it but little.

THE NOSE AND BRONCHIAL ASTHMA

Voltolini's report of a cure following nasal operation was not substantiated by later observation.[27] Since then, however, nose specialists have done their share in the treatment of patients with bronchial asthma, but they have not been able to achieve a permanent cure in these cases.[28] It is gratifying to read the clear expression of Lord in his chapter on bronchial asthma on the relation between diseases of the nose and asthma. "It is sufficiently obvious that asthma is not always caused by nasal disease, and that nasal disease is more often unaccompanied by asthma than the contrary." [23] Nasal pirates alone (to use an expression of Dr. Max Kahn) proclaim their personal successes in this field, suggesting their own superiority in the treatment of these patients. It is becoming recognized that nasal operations are not of permanent avail in true bronchial asthma.[29]

Analyses of series of cases have shown that operations on the nose in the treatment of bronchial asthma are ineffective.[30]

METABOLISM IN ASTHMA

Regarding the metabolism of asthma, a number of careful studies have been made. Rosenbloom, in one case, found that the metabolism of nitrogen was normal; the urea, ammonia, creatinine, uric acid, amino acids, and undetermined nitrogen were normal in amount and in per cent of the total nitrogen. The sulphur metabolism was also normal. The total sulphate sulphur, inorganic sulphate sulphur, ethereal sulphate sulphur and neutral sulphur were also normal. There was a tendency for a loss of calcium in this patient. This was also true to a lesser degree regarding the magnesium and phosphorus. Rosenbloom surmised that the value of calcium in the treatment of bronchial asthma bears some relation to the loss of calcium in this condition.[31]

26. Rackemann: Am. J. M. Sc. **163**:87 (Jan.) 1922.
27. Voltolini: Proc. Laryng. Soc., London, 1899, p. 83.
28. Adam: Asthma and Its Radical Treatment, New York, Paul B. Hoeber, 1913.
29. Krez: Wurzb. Abhandl. a. d. Gesamtgeb. d. prakt. Med. **14**:213, 1914.
30. Walker: Studies of the Cause and Treatment of Bronchial Asthma, J. A. M. A. **69**:363 (Aug. 4) 1917. Kahn: Nasal Operations in Bronchial Asthma, J. A. M. A. **82**:536 (Feb. 16) 1924. Lintz: Ann. Surg. **79**:917 (June) 1924. Heatley and Crowe: Bull. Johns Hopkins Hosp. **34**:410, 1923. Rowe: The Treatment of Bronchial Asthma, J. A. M. A. **84**:1902 (June 20) 1925.
31. Rosenbloom: Interstate M. J. **26**:174 (March) 1919.

Kahn and Zugsmith, in a more general study of the metabolism, found that persons who have asthma suffer from a condition of tissue suboxidation. The neutral sulphur fraction increase showed this lack of oxidation. The creatinine output was low, thus indicating a lessened tissue oxidation.[32] Various other observers noticed a decrease of tissue oxidation in dyspneic animals.

"CURE" OF ASTHMA

In general, the implication of absolute cure or of permanence of results is too often made in the literature on bronchial asthma. Thus such statements occur as "A positive skin test is a necessary preliminary to successful specific treatment." [33] "Nearly 9 per cent of patients are entirely freed of their symptoms. These results were determined by a personal communication to each patient four to six weeks after the ragweed season"; [34] and again, "the patients who gave a positive test to their own organism were treated with this organism, all of them with success." A subsequent paragraph in this paper qualifies, "The permanency of the favorable results obtained is as yet to be discovered, but most of these patients have retained, at least during the seven months of observation, the result which followed the treatment as given." [35]

I may say that since 1916, work has been done using autogenous defibrinated blood in the treatment of bronchial asthma.[36] In later reports, the results obtained were as favorable as those with any other method, such as vaccine, attempts at desensitization and even change of climate.[37] This method, therefore, far from being important as a measure of treatment, has the same value as any other method as far as the possibility of absolute cure of asthma is concerned.

Before the present methods of treatment were so generally utilized, equally "successful" results were recorded by Salter [38] in carefully studied cases observed over a long time. Thus, recording his remarks in different cases under the heading Effects of Remedies:

> Principal remedy, smoking pure tobacco, attending strictly to diet, avoiding everything that disagrees, and choosing a locality that suits. Different rooms even make a difference to me. By these rules I have cured myself. . . . Seven years ago tried Locock's wafers, and soon greatly improved. During the second year had but one attack, and that in a thunder storm. Since then, five years entirely free. Can do anything."

32. Kahn and Zugsmith: Metabolism of Asthma, Arch. Int. Med. **21**:510 (April) 1918.
33. Rackemann: Bronchial Asthma, Arch. Int. Med. **22**:517 (Oct.) 1918.
34. Rackemann: Boston M. & S. J. **182**:295 (March 18) 1920.
35. Rackemann: J. of Immunol. **5**:376 (July) 1920.
36. Kahn and Emsheimer: Autogenous Defibrinated Blood in the Treatment of Bronchial Asthma, Arch. Int. Med. **18**:445 (Oct.) 1916.
37. Henske: J. Missouri M. A. **18**:431 (Dec.) 1921.
38. Salter: On Asthma, New York, William Wood & Co., 1882.

Apparently permanently cured himself by walking 20 miles a day. . . . . Was prescribed a slight regular aloetic purge, tonics, an early dinner and nothing after it, plain, spare diet, avoidance of unwholesomes. Cure complete. . . . A blister or other counterirritant to the chest soon relieves. A rhubarb pill three times a week useful. No attack for from six to eight months. . . . Dietetic rules have given an almost perfect cure. . . . Pill containing ext. stramonium, grain ¼, hyoscin, grain 1½, and conium, grain 1½, completely put a stop to the night paroxysms and cured the case. . . . Chloroform the only thing that has done good. Morphia does harm. Other remedies worthless. Cured by London air. . . . Gin and water always cures. . . . Coffee and emetics always relieve; niter-papers at first; hot spirits for a time. Change of air to France always cures. . . . A mixture containing tincture of opium, sulphuric ether and compound tincture of lavender cures like magic. . . . Cured by dieting. . . . Completely cured by leaving off meat at dinner. . . . Free purging and raw gin the only remedies. Change from healthy to an unhealthy air has cured. . . . Joy's cigars do great good; an ordinary cigar slight; emetics and stramonium temporary; coffee and chloric ether none. India cures. . . . Cured by iodide of potassium. Chloroform relieves, but prostrates. Niter-paper the only other remedy. . . . Iodide of potassium has cured. . . . Emetics always do good; niter-papers slightly. Finally cured by iodide of potassium.

In my own experience, so inconstant are the results with various methods of treatment that I propose to patients the use of a number of methods at the same time, or one method following the other, while I hold the case under observation and further study. These methods include the injection of autogenous sputum vaccine, the injection of a nonspecific protein, the treatment of any infectious foci such as sinuses, tonsils or teeth, antiasthmatic medication-epinephrine hydrochloride hypodermically for the attacks, potassium iodide as a thyreotropic sympathetic stimulant, belladonna as a vagus depressor, autogenous defibrinated blood and any other protein injection to which the patient's skin may react.

It is evident that I do not decry the use of these measures if a better method cannot be found.[39] I do not believe, however, that other physicians who are doing the same thing and I are making efforts entirely in the right direction. Physicians are led as much by any new measure, as if they did not conceive of the underlying basic phenomena that must be considered in bronchial asthma.

ABSOLUTE CURE IN BRONCHIAL ASTHMA

In reply to an inquiry on the curability of bronchial asthma recently sent out to the workers most prominent in this field in the United States, replies with permission to publish them were obtained from those whose experience is most to be considered. A few others regretted their inability to answer the queries on the ground that it would be giving their opinions to a profession not yet prepared to receive them. Their

39. Ortner: Vorlesungen über Spezielle therapie Immer Krankheiten, Vienna, W. Braunmuller, 1923.

names are therefore considerately omitted from this article. The following are abstracts of the letters; I have taken great care to include in each the context so as to give their essence fully:

Dr. Mark J. Gottlieb, New York: I can only say that in my experience, which runs over a period of twelve years, absolute and permanent cures of asthma were unobtainable.

I am in accord with most of the conscientious workers in this field when they say that the disposition to asthmatic attacks is inherent in the constitution of the individual when he or she is born, and that fundamental quality cannot be changed.

I have in my files a number of cases which I have followed for periods free from symptoms running from twelve to five years, but even these may from time to time have recurrences of their malady due to the acquisition of new respiratory infections, intestinal upsets or disturbances generally which cause a malfunction of elements which control the involuntary musculature of the body, particularly the muscles of the bronchi and bronchioles.

I have no objection to the use of my name under this statement, for I know that it summarizes as truthfully as is possible the facts as I find them.

Dr. George Piness, Los Angeles: If I knew what you meant by an "absolute cure" of bronchial asthma I think I would be in a better position to answer your questionnaire, but since I do not know what it means, I cannot do so. In my experience of almost ten years in allergic work, during which time I have done nothing else, I have many patients who have been free over this period of time, others for a shorter period of time, but I cannot say offhand how many have been entirely free during the years they have been under my care. Personally, I do not believe that one can say that an asthmatic is ever permanently cured, because of the peculiar etiology which is so well known to you. I believe that the term "free from symptoms" should be used instead of "cured."

Dr. Francis M. Rackemann, Boston: I know that I have one or two absolute cures and it may be many more, because occasionally somebody comes in who tells me that they know of a former patient of mine, who, since taking treatment, has had no further asthma.

Dr. Henry Sewall, Denver: I can only say that this environment seems to be astonishingly remedial in certain typical cases in which the patient comes here from other climates, as Chicago; but I have seen considerable numbers of asthmatic sufferers who seemed as badly off here as elsewhere. The whole problem is most fascinating, and I know none whose consideration is more likely to be warped by mental preconceptions.

Dr. F. W. Gaarde, Rochester, Minn.: Owing to the fact that our patients come, as a rule, from such great distances, and because of the difficulty in obtaining reliable reports in answer to letters of inquiry, I am unable to give you the information you ask concerning our results in asthma.

We can get a general idea as to the patient's condition, but to have a definite statement as to positive cures is too uncertain a thing to warrant placing in statistics. I am sure that you realize that we are situated differently from the physician who is in constant close touch with his patients.

Dr. Andrew C. Henske, St. Louis: I suppose you have reference to the treatment with autogenous defibrinated blood. In the past ten years I have treated about thirty patients by this method. In this series there are only five patients to my knowledge who have remained absolutely free from symptoms for over a period of five years or more. Ten others derived temporary benefit, and the balance apparently no relief at all.

My experience with the protein sensitization tests and treatment after the method of I. Chandler Walker has been unsatisfactory.

In fact, I have had few permanent results from any one method of treatment. On the whole, would say that despite the optimistic reports found in

the current literature, the question of curative treatment of bronchial asthma is still an unsolved problem.

DR. CHARLES H. EYERMANN, St. Louis: One can interpret the term cure in two ways, first, symptomatic cure and second, disappearance of positive skin tests.

I will answer the second question first by saying that I do not recall a case in which the skin tests disappear despite absence of symptoms, whether as the result of treatment or mere avoidance of contact. However, positive skin reactions do disappear as exemplified by a lad of 13, who has had the classical sequence of eczema, urticaria and asthma, who as an infant gave unmistakable positive reactions to egg white. He now gives no reaction to egg white, but reacts to many other substances, and he still has eczema, hay-fever and asthma.

I have had several asthmatic patients under observation for a number of years, the longest since 1919, who have remained symptom-free as long as they have avoided the offending protein. None of these patients have had specific treatment; all have taken care of themselves by avoiding contact. One of these, just recently had an attack of asthma by the ingestion of the offending protein, wheat. A second one, whose condition was also caused by wheat, is now able to eat wheat apparently in any quantity without having asthmatic attacks. However, inhalation of flour dust produces vasomotor rhinitis and, if in sufficient concentration, asthma ensues. I have not treated asthmatic patients with specific substances when it has been possible for them to avoid these substances, which has been the case in the majority of instances. Such patients consider themselves cured, because they can control their symptoms or be free from asthmatic attacks by avoiding contact, although from an immunologic point of view, they are not cured. I have observed two cases of a definite bronchospasm, not giving positive cutaneous reactions, in which the patients have remained free from their asthmatic attacks for a period of two years, while tuberculin was being administered. These patients are still being treated with an occasional injection of tuberculin. These certainly are cured from the patient's standpoint. I cannot say definitely whether they are or not.

I have also had experience in observing persons with seasonal asthma in whom, following preseasonal and proseasonal pollen injections, there have been no asthmatic attacks. They have also continued having hay-fever symptoms of greater or less degree. Again, a cure from the standpoint of the patient.

I cannot give the percentages of cures as judged by the foregoing, for I have not compiled all the cases that I have seen.

DR. F. M. POTTENGER, Los Angeles: I cannot give you any information as to the absolute cure of asthma. It is only recently that I have taken into my institution any patients suffering from asthma, who did not have complicating tuberculosis; so I cannot give you a large series under any circumstances. I have found that by the methods we use, we have been able to relieve about 50 per cent of the patients. This is simply a rough estimate.

DR. I. CHANDLER WALKER, Boston: I cannot give you absolute statistics regarding cures of asthmatic persons. Some marry and change their names and address, many move and some do not answer questionnaires. Therefore, it is impossible to follow many patients.

In my office, I feel sure more than 75 per cent of persons with vaccine cases have their asthma stopped for the remainder of the winter. Many, however, have to be treated the next fall in order to be free for the succeeding winter. I do not know how many are cured for years, but every week I usually hear of from three to four old cases that I treated with vaccine three or four or five years ago, and these have been free from asthma ever since, so that I get considerable encouragement that many asthmatics are cured for several years at least by one or two courses of vaccine. I have many patients with pollen cases who have remained free from asthma for two, three, four, or five years, following two or three years preseasonal pollen treatment, but I could not

possibly tell the percentage. Failures, however, are rare for the season immediately following a course of treatment.

Failures in food sensitive and animal sensitive cases are rare, and I do not know of more than two or three such cases in which there has ever been a relapse, and these few have become bacterial cases and the patients have been cured by vaccine treatment.

DR. ALBERT VANDER VEER, JR., New York: I am very sorry, but I do not think we can give you any definite figures which would be of any value on the absolute cure of bronchial asthma. We avoid the term intentionally, substituting the words "relief of symptoms," and even using this terminology, it is difficult to state in percentages what our results are. With the asthma cases due to pollen it is of course comparatively easy because if the patient is free during his season, under tr[illegible]ent, and exposed, we may consider him relieved of symptoms and the [illegible]entage in these cases is about 80. Patients sensitive to animal epithelia are of course free from asthma as long as they are not exposed to the animals in question. Patients who have had horse asthma whom we have treated, almost invariably do well, and as a guess, I should say that the percentage of freedom from symptoms was between 80 and 90, but this is only a guess. Patients with asthma due to chronic sinus infection are, of course, the most difficult to treat, and while in the majority the condition clears up under treatment, they are likely to have a recurrence.

DR. W. W. DUKE, Kansas City: Success in treating asthma depends, of course, on the cause. Of pollen cases, last year I cured 100 per cent of patients in which the condition was not complicated with sensitiveness to heat or cold. A small number of pollen cases are complicated by this condition, and in this case are more difficult to get rid of symptoms completely. Furthermore, symptoms are inclined to continue during the winter months when this is the case. Of perennial cases and seasonal cases caused by sensitiveness to cold, I think all patients were made symptom-free with relatively simple measures.

Of the patients sensitive to heat, I think we relieved a little more than 50 per cent. In cases of combined sensitiveness to heat and cold, we were perhaps less fortunate, but this does not include a large per cent of cases as they come to a doctor's office. They are, however, extremely severe cases.

Of the miscellaneous group of cases which we traced to some tangible substance, I think we have relieved all, either through avoidance of cause or with treatment with the specific agent responsible for the illness.

I am highly enthusiastic over the results which can be accomplished by therapy in asthma if the case can be worked out along broad lines. I believe, however, success depends on a broad study of a case with treatment as indicated by the result of examination.

It will be seen that opinions range from the belief that absolute permanent cure in asthma is unobtainable (Gottlieb) to an assertion of 100 per cent of pollen cases cured (Duke).

In his letter as in his writing, Duke uses the term "cure" but not in the sense of complete or absolute cure in which the patient does not require any further treatment. He says a rather large proportion of persons inherit a constitution which makes it possible for them to become hypersensitive to foreign substances. Once sensitive, they are likely to react in characteristic ways whenever they come in intimate contact with the substances to which they are sensitive.[40]

40. Duke: Food Allergy as a Cause of Illness, J. A. M. A. **81**:886 (Sept. 15) 1923.

It is apparent, therefore, that the term "cure" is used with different significations by the various writers. In some replies, cure is assumed to be synonymous with temporary relief from symptoms. Since such temporary relief is often spontaneous, a great deal of the success attributed to treatment must be discounted.

The term "cure" is definite in its significance. It means to heal, to restore to sound health, to subdue or remove an ailment by remedial means. A method of treatment or a medicine cannot be held to be a cure if it does not entirely eliminate the disease from the body. We do not speak of a cure of Hodgkin's disease, or of cancer, or of diabetes mellitus unless the pathologic background of the condition is effaced and the person continues to maintain normal health without further treatment. It is in this way that we must apply the term "cure" to bronchial asthma. And, thus far, by all the methods that have been created, a cure has not been discovered.

Walker's letter represents his opinion substantially as do his excellent contributions to the literature on the subject.

Piness' letter contrasts somewhat with the following conclusions expressed by him in an earlier paper: [41]

> The hypersensitive state may be present at birth, inherited, or conveyed by the mother to the child. A history of eczema, urticaria, or hay-fever bears a definite relationship to the protein sensitive asthmatic. Bronchial asthma is no longer an incurable condition, since by scientific study with cooperation on the part of the patient and persistency on the part of the physician, the greater percentage of sufferers can be permanently or partially relieved.

HEREDITY IN BRONCHIAL ASTHMA

In an article on the curability of asthma, Tracy paints a background of hereditary susceptibility to asthma, and then proceeds to advise measures to alter the constitution and metabolism of the person.[42] The means he advocates are radical change in the patient's intellectual groundwork, change in the patient's surroundings, change of his intestinal flora and radical change in food, both in kind and quantity, and a change of life's habits; he hopefully concludes that "bronchial asthma is curable." Recognizing that measures of constitutional treatment of bronchial asthma are visionary, and unpractical, he justifies their use by "the inadequacy of symptomatic treatment, and the consequent opprobrium to medicine."

The importance of constitutional predisposition and the conspicuousness of the family tendency in this disease has long been recognized.[38]

The bronchial constriction in the attack is aroused either peripherally, reflexly or directly from the central nervous system. It can hardly be

41. Piness: Southwestern Med. **6**:287 (Aug.) 1922.
42. Tracy: New York M. J. **105**:149 (Jan. 27) 1917.

doubted that, given a certain predisposition, asthmatic attacks are brought about in all these ways.[43]

The significance of heredity is tersely asserted by Coca when he defines allergy as "A natural inherited condition of hypersensitiveness which affects only human beings and is not dependent in any way on immunologic antibodies." [8]

STATISTICAL ANALYSES

In the analyses of cases of bronchial asthma, the family history, often recorded as negative, is based on fallacious data. On closer investigation, it will be found, as I shall now demonstrate, that most of these patients do not adequately know their family history. In a careful tabulation, it will be found, as Talbot found in his series of nineteen children, that all patients have a positive family history.[44] The subject therefore changes its field of interest from the anaphylactic one to the study of the germ cells and their genetic characters. The study of hereditary tendencies in human beings cannot be achieved alone by the family anamnesis of the person, since the ancestry of the family is usually known for only one entire generation. The results appear capricious because the ancestral history as given is often recorded as fact, when in reality it is not known.

In the statistical discussion on heredity in the series of 350 cases reported by Coke in England, asthma is shown to be comparatively rare, occurring in a well-marked form in perhaps from 1 to 500 of the population.[45] Of the whole series of 350 cases, 162, or 46 per cent, gave a family history of asthma and hay-fever; seventy men and ninety-two women. Of the 182 patients who were sensitive, 103, or 56 per cent, gave positive family histories, and seventy-nine, or 44 per cent, did not; 109 patients gave neither family history nor any dermal reactions.

Analyzing his records, sixty-three parents had asthma, seventeen true seasonal hay-fever, fourteen eczema or urticaria, six migraine; sixty-five patients had brothers or sisters with asthma, hay-fever, eczema; and fifty-nine patients had one or more grandparents who had asthma or hay-fever.

The outstanding feature of supreme importance in these cases is their hereditary tendency. About 50 per cent of the cases studied by Salter,[38] Rackemann,[33] Adkinson,[46] and Cooke and Vander Veer [47] gave a hereditary history in the diseases or in associated conditions such as

43. Goodhart and Spriggs: In Allbutt and Rolleston's "System of Medicine," **5**:54, 1909.

44. Talbot: Boston M. & S. J. **175**:191 (Aug. 10) 1916.

45. Coke, F.: Asthma, New York, William Wood & Co., 1923.

46. Adkinson: The Behavior of Bronchial Asthma as an Inherited Character, Genetics **5**:363 (July 5) 1920.

47. Cooke and Vander Veer: J. Immunol. **1**:201 (June) 1916.

eczema, urticaria, hay-fever and others. From their studies, it became evident that the theoretic requirements of the mendelian law are approximated. The analysis of Cooke and Vander Veer suggested that sensitization is inherited as a dominant characteristic.

Sensitive cases are more likely to give positive family histories.[48]

In dealing with human beings the conditions are not precise enough for absolute accuracy. It is not possible to be sure that a person is pure-sensitized or mixed. If the sensitization trait is pure in one parent, all the offspring should be sensitized whether the trait in the other parent is pure or mixed.

In regard to those cases of asthma in which there is an absence of sensitization in the family history, nothing can be said. In can only be surmised that here the failure to find the antecedent sensitization was owing to the limitations of the methods of ascertaining the family histories in this respect.

Of 144 patients with bronchial asthma under my observation, I obtained a positive history in seventy cases, or 48 per cent, and a negative history in seventy-four cases, or 52 per cent. Taken at their face value, these figures are parallel to those obtained by most other workers in this field.

I hold, however, to the belief that these figures cannot be taken to mean what is usually implied for the following reason: Of the seventy-four cases with a negative history, the largest number showed a markedly incomplete knowledge of their ancestry or their lateral kin. A large proportion of these also were members of numerically small families from which, of course, data should not be used for statistical purposes. Moreover, a number of these histories must be considered unreliable when they are negative, whereas a definite positive hereditary history is not questionable.

Other interesting figures analyzed from the group of seventy positive cases are as follows: There were thirty-six men who had asthma and thirty-four women. Inheritance was from the father in twenty-one cases, of which twelve of the patients were men and nine women. Inheritance was from the mother in twenty-two cases, of which nine of the patients were men and thirteen women. It is to be seen that forty-three cases, or 61 per cent, were transmitted from the immediate parentage, suggesting the asthma in these cases to be a dominant factor in the mendelian sense. This is increased by the group of eight other patients who had children affected with asthma, making the percentage of dominant transmission seventy-three. There were nine cases of inheritance from grandparents. This number is augmented by additional

48. Longcope: Protein Hypersensitiveness and Its Importance in the Etiology of Disease, J. A. M. A. **77**:1535 (Nov. 12) 1921; Am. J. M. Sc. **152**: 625 (Nov.) 1916.

ten cases in which the inheritance was through lateral kin; that is, in nineteen cases, or 27 per cent, the asthma was a recessive factor. Twenty-four patients had brothers or sisters with asthma or hay-fever.

The general principles expressed by Cooke and Vander Veer are based on careful analyses. I believe, however, that in reasoning from statistics there is always the danger of introducing fallacies. The important conclusion from their studies is that artificial sensitization is not easy to accomplish. Natural sensitization is transmitted to offspring as an unusual capacity for developing bioplastic reactivities to any foreign protein. The term "cure" is incorrect and misleading, and therefore should not be used in any discussion of results. The protection afforded by active immunization should not be expected to be permanent in any sense. These patients do not return to a normal state as a result of any form of treatment. The final solution in discovering the genesis of bronchial asthma lies in the phenomena of heredity.

SUMMARY

Reports of the benefit derived from the various methods of treatment of bronchial asthma are extremely diverse. Thus far, no method of treatment seems to have greatly influenced the course of the disease, which is naturally variable.

In its etiology, anaphylaxis may be dismissed from consideration. Protein sensitization is indeed a phenomenon in this disease, but it apparently is not the basic cause of the condition. It is true that the sensitization tests indicate intoxication by some substance or substances, usually protein in nature; but treatment for purposes of desensitization or immunization is futile in the endeavor to obtain an absolute cure.

The relation of nasal disease to asthma shows evidence of a constitutional susceptibility rather than a causal relationship, just as do vagotonia, hemoclasic crises and all the other theories thus far advanced as causative of asthma.

The final solution in discovering the genesis of bronchial asthma lies in the phenomena of heredity. The condition is rooted in the biologic and physicochemical structure of the chromosomes. A hereditary factor is present, not in a certain fraction of the cases, but in 100 per cent of the cases. The fallacies of statistics on heredity in human beings are well established and depend mainly on the insufficient knowledge of ancestry in cases of bronchial asthma.

CONCLUSIONS

An absolute cure of asthma is, therefore, not to be expected until a method has been found which will alter the chromosomal constitution either in the adult or, more radically, in the genetic cells.

ETIOLOGIC FACTORS IN DIABETES

PAPER II

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In a preceding article, the subject of hereditary tendency in diabetes [1] was discussed, with the concluding thought that diabetic patients present certain physical characteristics, and that these characteristics in reality are constitutional watermarks.

In searching further for etiologic factors in diabetes, I made a survey of all preceding diseases in a group of 226 diabetic patients. This survey deals especially with infectious diseases experienced prior to the onset of diabetes, and is part of a general study concerning the relationship of acute infection to chronic diseases.

To this end, a statistical study of the history of the disease was made in 1,530 unselected medical cases. From these patients my co-workers and I obtained a complete history of all the known previous diseases. Each patient was given a questionnaire to be filled in at home, with the assistance of the family, which we believe increases the accuracy of such records.

The type and proportion of the various diseases diagnosed in these 1,530 patients are shown in the table.

INCIDENCE OF VARIOUS DISEASES IN PATIENTS STUDIED

Diabetes	226
Gastro-intestinal diseases	192
Neuroses	177
Cardiovascular (organic) diseases	171
Endocrine disturbances	156
Arterial hypertension	143
Pulmonary infections	135
Focal infections	110
Diseases of nutrition	96
Acute and subacute nephritis	67
Syphilis	57
	1,530

Chart 1, which gives the frequency curve of all diseases, was constructed from the tabulated results of these records.

As will be seen, measles was the most common of the acute infections; this was followed by pertussis and varicella. Next in frequency was tonsillitis, although higher figures for tonsillitis would not have been

1. Barach, Joseph H.: Constitutional and Hereditary Traits in Diabetics, Am. J. M. Sc. **172**:243 (Aug.) 1926.

surprising. It is assumed that the figures in the table indicate those cases in which attacks were recurrent and troublesome. The figures for influenza probably include some cases of the grip, the terms being used interchangeably by both physician and patient. Those for typhoid fever may seem high; this is due to the fact that for many years typhoid fever was pandemic in Pennsylvania and adjacent states. The charts include tonsillectomy for the purpose of indicating tonsillar disease sufficiently troublesome to warrant operation. Surgical operations and serious

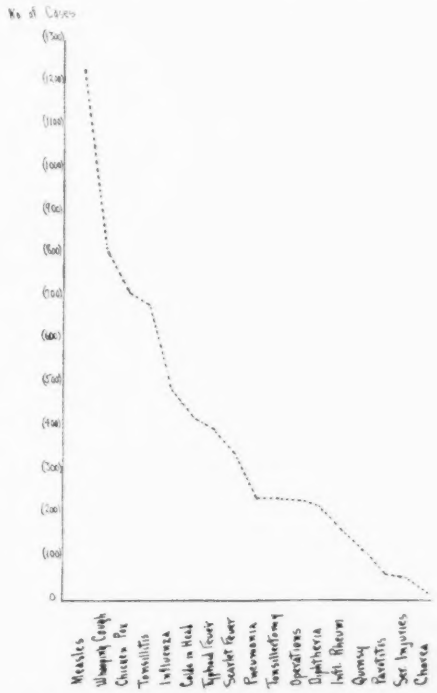

Chart 1.—Curve for all diseases—1,530 cases.

injuries are also recorded. As the chart shows, the curve is arranged on the basis of frequency, the most common infection first, and the least frequent ones last.

Neuroses.—For the purpose of comparison with chart 1 for all diseases, a curve is shown made up of a mixed group of 177 cases classified as neuroses (chart 2). These patients were free from other discoverable disease. They were cases of psychasthenia, neurasthenia, psychoneuroses and neurocirculatory asthenia. Diagnoses were made after organic diseases had been eliminated as far as possible, and when it was impossible

to make more definite diagnoses. It is interesting to note how well this curve of the nondescript group corresponds to the all disease curve, exceeding it only in the greater number of tonsillectomies. This is explainable when one recalls how such patients go from one physician to another seeking relief, and are sooner or later advised to submit to tonsillectomy.

Pulmonary Infections.—Contrasted to the all disease group and the neuroses group, a curve based on a series of 135 cases of pulmonary

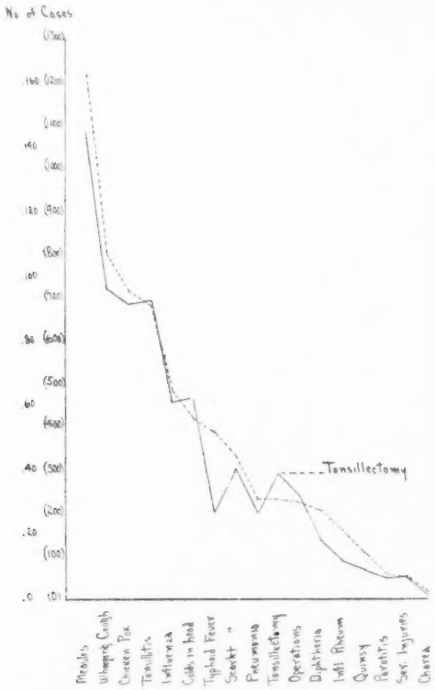

Chart 2.—A comparison of the all disease curve and the neuroses curve—177 cases. The broken line indicates the all disease curve; the unbroken line, the neuroses curve.

infections is presented (chart 3). This group includes tuberculous and nontuberculous pulmonary infections. It may be seen at a glance that the diseases in this group which exceed those of the all disease curve, correspond to the physician's daily experiences in this type of case. Tonsillitis, colds in the head and pneumonia are the characteristic complaints of patients with pulmonary disease.

Gastro-Intestinal Cases.—This group includes 192 gastro-intestinal cases. The curve of these gastro-intestinal cases exceeds the all disease

curve strikingly in the number of operations (chart 4). These operations were generally performed for diseases of the appendix, gallbladder, stomach or duodenum. The curve conforms well to what may be expected in this type of patient.

Diabetes.—In a group of 362 cases of diabetes, the diabetic curve shows an excess over the all disease curve in chronic tonsillitis and in typhoid fever (chart 5). I believe this to be of clinical significance. It is a striking experience to find enlarged and diseased tonsils in every

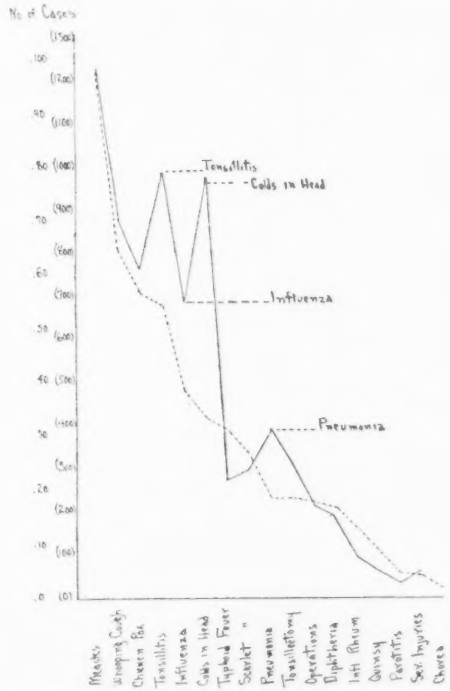

Chart 3.—A comparison of the all disease curve and the pulmonary infection curve, including 135 cases of tuberculosis, asthma and bronchitis. The broken line indicates the all disease curve; the unbroken line, the pulmonary infection curve.

third person with diabetes that one examines, the total number of cases being 114. In the last 226 cases of diabetes in which the previous history of the disease was complete, there was a history of recurrent tonsillitis and the presence of diseased tonsils at the time of physical examination in 107 cases, almost one half the total number. All this seems especially significant when one recalls that these persons have carried diseased tonsils into the fourth and fifth decade of life. A focal infection of

thirty or forty years' duration, even if intermittent, is injurious. This assumption is understood in the light of what is known of the insulin disturbance which occurs in patients with diabetes during acute infections of any kind.

Typhoid fever, as the curve clearly shows, had occurred in these diabetic patients with unusual frequency. That a relationship may exist between typhoid fever and diabetes is further suggested by the fact that a hyperglycemia is present in the course of the disease, and by evidences

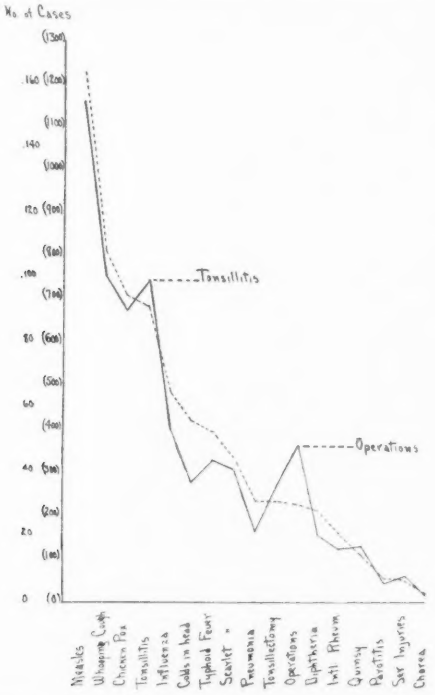

Chart 4.—A comparison of the all disease curve and the gastro-intestinal curve—192 cases. The broken line indicates the all disease curve; the unbroken line, the gastro-intestional curve.

of a definite metabolic change which follows convalescence from the disease. Posttyphoid obesity is just as striking as prediabetic obesity. It is possible that both are due to a similar underlying cause, some pathologic change in the insulin producing tissues.

SUMMARY AND DISCUSSION

In order to study the infections as possible etiologic factors in diabetes, a curve was constructed indicating the relative frequency of all

preceding infectious diseases in 1,530 patients. My co-workers and I compared disease frequency in a nondescript group of neurotic patients with the all disease curve and found no divergence in the curves. A group of cases of pulmonary infection shows that such patients suffer most frequently from tonsillitis, acute colds and pneumonia. A group of patients with gastro-intestinal diseases shows excess in operative cases, such as appendectomy, gallbladder, gastric and duodenal operations. These and other charts not included here show the validity of the all

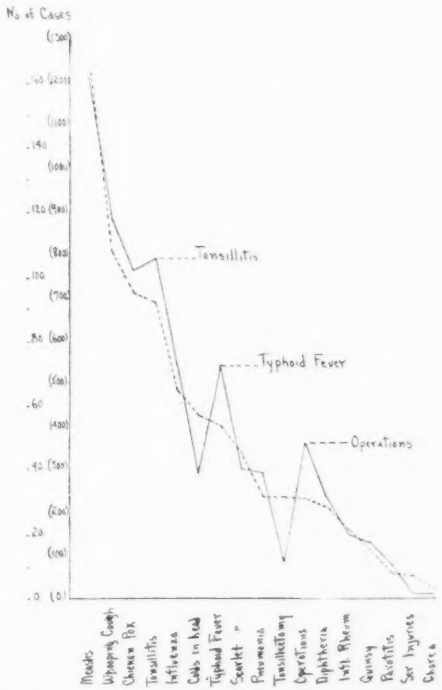

Chart 5.—A comparison of the all disease curve and the diabetic curve—226 cases. The broken line indicates the all disease curve; the unbroken line, the diabetic curve.

disease curve, and indicate that any marked deviation from this curve has definite clinical significance. The special group considered here, that of diabetic patients, shows a marked increase in the number of cases of chronic tonsillar disease and typhoid fever.

Attempting to interpret these two deviations from the all disease curve, my co-workers and I were led to believe that in chronic tonsillar disease repeated strain on the insulin-producing tissues, as must occur with each fresh attack, undoubtedly has its injurious effect. The con-

tinued effect of a chronic infection is less apparent. Typhoid fever is an acute infectious disease of such duration and severity as could be the cause of permanent injury to the pancreas and other tissues.

Physicians who treat diabetic patients in considerable numbers know that an intercurrent acute infection reduces carbohydrate tolerance to one half or even more than one half of the normal tolerance for that person. Whether strain on the insulin-forming tissues results from frequently recurring infections, or whether it results from a severe and prolonged acute infection such as typhoid fever, the strain imposed on an organism endowed with hereditary tendency to diabetes may be sufficient to transform the potential into a case of real diabetes.

RELATION BETWEEN CELL COUNT, CELL VOLUME AND HEMOGLOBIN CONTENT OF VENOUS BLOOD OF NORMAL YOUNG WOMEN

REDETERMINATIONS OF COLOR INDEX, VOLUME INDEX AND SATURATION INDEX STANDARDS BASED ON OBSERVATIONS IN ONE HUNDRED CASES *

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The need for a definite accepted figure, expressed in grams per one hundred cubic centimeters, as the standard of average hemoglobin content of normal blood has been emphasized recenty.[1] Few physicians, however, realize that the figures usually given in the texts for average normal red cell counts (5 million for men and 4.5 million for women) are apparently based on only four blood examinations made in 1852 [2] and 1854 [3] by methods which are now obsolete. These figures have since been copied from one textbook to another without experimental confirmation. The increasing use of volume index, saturation index and color index determinations in the differential diagnosis of anemia demands that the normal averages and ranges of variation in these observations be determined accurately.

In this article we present the results of accurate red cell counts, hemoglobin determinations and cell volume determinations on 100 healthy young women, and give the average and range of variation of the corresponding indexes.

As the methods used are identical in every detail with those used in a previous research on the normal standards in healthy young men, the details of the technic are omitted here, and the reader is referred to our previous article.[4]

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* From the Department of Biochemistry, University of Oregon Medical School.

1. Editorial: The Need for a Fixed Hemoglobin Standard, J. Lab. & Clin. Med. **11**:696 (April) 1926. Lindsay, J. W.; Rice, E. C., and Selinger, M. A.: A Plea for a Standardized Method of Estimating and Reporting Hemoglobin Values, ibid. **11**:737 (May) 1926.

2. Vierordt, K.: Zählunger der Blutkörperchen des Menschen, Arch. f. physiol. Heilk., Stuttgart **11**:327, 1852.

3. Welcker, H.: Ueber Blutkörperchenzählung, Arch. d. Ver. f. gemeinsch. Arb. z. Förd. d. wissensch. Heilk., Göttingen **1**:161, 1854.

4. Osgood, E. E.: Hemoglobin, Color Index, Saturation Index and Volume Index Standards, Arch. Int. Med. **37**:685 (May) 1926.

SUBJECTS EXAMINED

One hundred young women between the ages of 18 and 30 were studied. With the exception of a few medical students, all were nurses, which explains the slightly lower average age than that of the men studied.

Figure 1 shows at a glance the age distribution of the women and of the men studied previously. As there were no men 18 years of age in our series, we have noted the average of the results on the twelve women of this age separately for comparison (bottom of table 1). Note that they do not differ significantly from the averages for the total 100 cases.

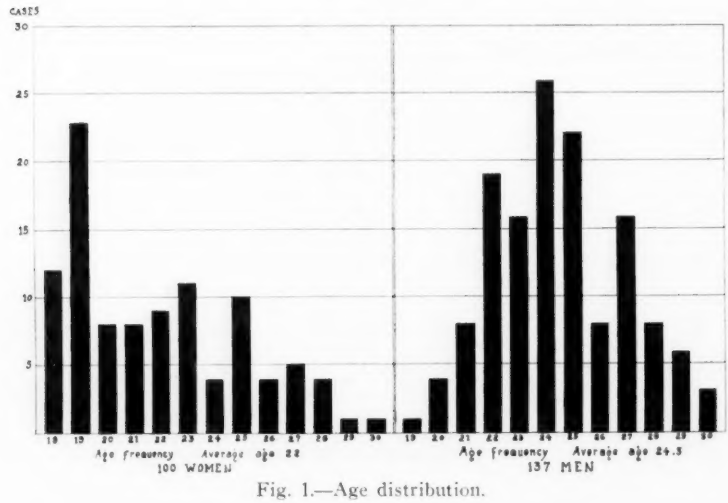

Fig. 1.—Age distribution.

For comparison we have also inserted the averages previously reported on 137 men between 19 and 30 years of age.[4]

Each of the subjects felt well at the time the blood was drawn, and as practically all of them had had a complete medical examination within a year, it is safe to say that they were in good health when examined. To avoid any possible temporary influence of menstruation on the results, examinations were not made during the menstrual period or during the week following it. The height, weight and nationality of each subject were recorded, but are not included in the table, as these data are not used in this article. The great majority were American born of American parents. Most of the others were American born of foreign born parents, including chiefly Irish, Scotch, English, Scandinavian and German. There were not enough of any one nationality to justify an analysis on this basis.

Most of the specimens of blood were drawn between 8 and 9 o'clock in the morning in the fall of the year. However, a particular effort was not made to take the specimens of blood at the same time of the day or year, as this is not done in clinical practice, and as we wished to determine the full range of normal variation. All the subjects examined reside at an altitude of less than 500 feet.

THE RED CELL COUNT IN NORMAL WOMEN

A survey of the literature to date (October, 1926) shows that reasonably accurate red cell counts have been reported for only eighteen normal women whose ages were specifically mentioned as being between 18 and 30. They are distributed as follows:

Bierring[5]: 3 women, averaging 4.24 million.
Gram and Norgaard[6]: 6 women, averaging 4.59 million.
Haden[7]: 9 women, averaging 4.33 million.
Total: 18 women, averaging 4.33 million.

The number of women studied is too small to impart any great significance to the average. In addition, the following presumably accurate counts on 194 women were found in the literature, but without any statement concerning ages:

Bie and Möller[8]: 10 women, averaging 4.74 million.
Bing[9]: 51 women, averaging 4.9 million.
Gram[10]: 56 women, averaging 4.78 million.[11]
Larrabee[12]: 9 women, averaging 4.97 million.
Six other authors[13]: 68 women, averaging 4.81 million.
Total: 194 women, averaging 4.83 million.

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5. Bierring, K.: Svingninger i Erythrocyttallet hos normale Mennesker, Ugesk. f. Laeger **82**:1445 (Nov. 18) 1920.

6. Gram, H. C., and Norgaard, A.: Relation Between Hemoglobin, Cell Count and Cell Volume in the Venous Blood of Normal Human Subjects, Arch. Int. Med. **31**:164 (Feb.) 1923.

7. Haden, R. L.: The Normal Hemoglobin Standard, J. A. M. A. **79**:1496 (Oct. 28) 1922; Accurate Criteria for Differentiating Anemias, Arch. Int. Med. **31**:766 (May) 1923.

8. Bie, V., and Möller, P.: Undersögelser af normale Menneskers Blod, Ugesk. f. Laeger **75**:749, 817 and 878, 1913; Le sang humain normal, Arch. d. mal. du coeur **15**:177 (April) 1922.

9. Bing, H. I.: On the Number of Red Blood Corpuscles at Different Ages and Under Different Circumstances, Proc. Ninth Northern Congress Int. Med., Acta med. Scandinav. **53**:833 (Jan.) 1921.

10. Gram, H. C.: Om det normale Erythrocyttale og den normal Hemoglobinmaengde i Veneblod, Ugesk. f. Laeger **82**:1543 (Dec. 9) 1920; On the Standardization of Hemoglobinometers and Its Importance for Index Calculation, Acta med. Scandinav. **57**:27 (Nov.) 1922.

11. Gram states that his subjects were nurses; so it is probable that his age distribution was similar to ours. Note the close agreement of our average figure (4.8) with his (4.78).

12. Larrabee, R. C.: The Volume Index of the Red Corpuscles, J. M. Research **24**:15 (Jan.) 1911.

13. Quoted by Bie and Möller (footnote 8).

The close agreement of this average with our average (4.8) suggests either that these workers chose subjects in the same age group as ours, or that there is little variation with age of the average red cell count in normal adult women. These reported counts range from 4 million to 5.9 million. Our lowest count was 4.07 million, and the highest was 5.55 million.

TABLE 1.—*Blood Observations in One Hundred Normal Young Women*

Subject	Age	Red Cell Count, Millions per C.mm.	Hemoglobin, Grams per 100 Cc.	Hemoglobin per 100 Cc. per 5 Million Cells	Color Index	Volume of Cells per 100 Cc.	Volume of Cells per 100 Cc. per 5 Million	Volume Index	Saturation Index
1	22	4.63	10.98	11.86	0.83	35.29	38.11	0.89	0.93
2	32	5.00	12.27	12.27	0.86	36.96	36.96	0.86	1.00
3	21	4.73	12.09	12.78	0.89	38.54	40.74	0.95	0.94
4	22	4.91	12.67	12.90	0.90	42.63	43.42	1.01	0.89
5	25	4.65	12.08	12.98	0.91	37.02	39.80	0.93	0.98
6	23	4.53	11.81	13.04	0.91	35.18	38.83	0.91	1.00
7	18	5.00	13.04	13.04	0.91	38.28	38.28	0.89	1.02
8	20	4.38	11.45	13.08	0.91	36.52	41.69	0.97	0.94
9	23	5.22	13.66	13.09	0.92	42.21	40.43	0.94	0.98
10	19	5.13	13.50	13.15	0.92	41.18	40.13	0.94	0.98
11	18	5.15	13.70	13.30	0.93	40.05	38.88	0.91	1.02
12	19	4.75	12.74	13.41	0.94	41.90	44.10	1.03	0.91
13	25	5.38	14.43	13.42	0.94	44.16	41.04	0.96	0.98
14	27	5.18	13.91	13.43	0.94	41.32	39.88	0.93	1.01
15	26	4.39	11.81	13.45	0.94	37.27	42.46	0.99	0.95
16	19	5.00	13.48	13.48	0.94	41.37	41.37	0.97	0.97
17	26	5.26	14.19	13.48	0.94	44.36	42.17	0.99	0.95
18	19	5.24	14.17	13.52	0.95	43.90	41.89	0.98	0.97
19	19	5.51	14.93	13.55	0.95	44.05	39.97	0.93	1.02
20	24	4.94	13.40	13.56	0.95	44.87	45.42	1.06	0.90
21	25	4.22	11.47	13.59	0.95	39.47	46.77	1.09	0.87
22	23	4.64	12.65	13.64	0.95	41.65	44.88	1.05	0.90
23	23	5.08	13.86	13.64	0.95	40.51	39.87	0.93	1.02
24	19	5.22	14.27	13.67	0.96	40.00	38.31	0.90	1.07
25	22	5.51	15.07	13.67	0.96	45.22	41.03	0.96	1.00
26	19	5.00	13.68	13.68	0.96	42.08	42.08	0.98	0.98
27	18	4.85	13.29	13.70	0.96	42.43	43.74	1.02	0.94
28	25	4.07	11.15	13.70	0.96	37.50	46.07	1.08	0.89
29	19	4.82	13.26	13.76	0.96	42.08	43.65	1.02	0.94
30	25	5.22	14.38	13.77	0.96	42.25	40.47	0.95	1.01
31	32	5.55	15.30	13.79	0.96	43.70	39.37	0.92	1.04
32	19	5.05	13.98	13.84	0.97	42.50	42.08	0.98	0.99
33	22	4.75	13.18	13.87	0.97	40.26	42.38	0.99	0.98
34	23	4.56	12.70	13.92	0.97	37.18	40.77	0.95	1.02
35	21	5.30	14.77	13.93	0.97	43.54	41.08	0.96	1.01
36	37	5.21	14.53	13.95	0.98	41.08	39.42	0.92	1.07
37	26	4.96	13.86	13.97	0.98	42.00	42.34	0.99	0.99
38	19	4.78	13.30	13.97	0.98	40.10	41.95	0.98	1.00
39	20	4.74	13.26	13.99	0.98	41.45	43.73	1.02	0.96
40	25	4.67	13.08	14.01	0.98	39.84	42.66	1.00	0.98
41	30	4.81	13.48	14.02	0.98	42.04	42.70	1.00	0.98
42	18	4.80	13.47	14.03	0.98	42.25	44.01	1.03	0.95
43	21	4.43	12.53	14.14	0.99	39.25	44.30	1.04	0.95
44	21	5.22	14.77	14.14	0.99	42.57	40.78	0.95	1.04
45	20	4.74	13.43	14.16	0.99	42.07	44.37	1.04	0.95
46	27	4.80	13.59	14.16	0.99	39.84	41.50	0.97	1.02
47	20	4.91	13.97	14.22	0.99	41.73	42.50	0.99	1.00
48	21	4.93	14.05	14.25	1.00	40.91	41.49	0.97	1.03
49	28	4.64	13.25	14.28	1.00	40.77	43.93	1.03	0.97
50	21	4.89	13.99	14.31	1.00	42.82	43.78	1.02	0.98
51	19	4.88	13.97	14.31	1.00	40.61	41.61	0.97	1.03
52	23	4.14	11.87	14.35	1.00	37.92	45.80	1.07	0.93
53	19	4.80	13.80	14.37	1.00	40.81	42.51	0.99	1.01
54	28	4.45	12.79	14.37	1.00	39.49	44.37	1.04	0.96
55	19	4.46	12.85	14.40	1.01	39.16	43.90	1.03	0.98
56	25	4.94	14.30	14.47	1.01	41.80	42.30	0.99	1.02
57	28	5.10	14.77	14.48	1.01	43.43	42.68	1.00	1.01
58	19	4.81	13.94	14.49	1.01	40.86	42.48	0.99	1.02
59	25	4.69	13.59	14.49	1.01	39.59	42.20	0.99	1.02
60	27	4.59	13.32	14.51	1.02	36.42	39.68	0.93	1.10
61	24	4.33	12.57	14.52	1.02	41.04	47.39	1.11	0.92
62	19	4.73	13.76	14.54	1.02	40.76	43.09	1.01	1.01
63	29	4.60	13.39	14.55	1.02	37.71	40.99	0.96	1.06
64	19	4.35	12.65	14.55	1.02	38.50	44.25	1.03	0.99
65	21	4.74	13.80	14.56	1.02	41.78	44.07	1.03	0.99

TABLE 1.—*Blood Observations in One Hundred Normal Young Women—Continued*

Subject	Age	Red Cell Count, Millions per C.mm.	Hemoglobin, Grams per 100 Cc.	Hemoglobin per 100 Cc. per 5 Million Cells	Color Index	Volume of Cells per 100 Cc.	Volume of Cells per 100 Cc. per 5 Million	Volume Index	Saturation Index
66	25	4.79	13.98	14.59	1.02	44.71	46.67	1.09	0.94
67	19	4.95	14.46	14.61	1.02	45.89	46.35	1.08	0.94
68	27	5.34	15.64	14.64	1.02	46.33	43.38	1.01	1.01
69	20	4.64	13.59	14.65	1.02	39.29	42.33	0.98	1.03
70	18	4.49	13.18	14.68	1.03	40.65	45.27	1.06	0.97
71	24	5.37	15.77	14.69	1.03	43.14	40.17	0.94	1.10
72	24	5.02	14.79	14.73	1.03	45.00	44.82	1.05	0.98
73	23	4.86	14.35	14.77	1.03	42.49	43.71	1.02	1.01
74	23	4.53	13.40	14.79	1.03	40.37	44.56	1.04	0.99
75	23	4.49	13.31	14.81	1.04	40.56	45.17	1.05	0.99
76	20	4.68	13.87	14.82	1.04	41.33	44.15	1.03	1.01
77	28	4.54	13.48	14.85	1.04	39.84	43.88	1.03	1.01
78	26	4.39	13.05	14.87	1.04	41.22	46.95	1.10	0.95
79	19	4.38	13.08	14.93	1.04	35.32	40.32	0.94	1.11
80	18	5.04	15.06	14.94	1.04	44.56	44.21	1.03	1.01
81	19	4.70	14.05	14.95	1.05	43.59	46.37	1.08	0.97
82	18	4.94	14.85	15.03	1.05	43.54	44.07	1.03	1.02
83	18	4.54	13.69	15.08	1.05	39.33	43.32	1.01	1.04
84	18	4.48	13.52	15.09	1.06	41.84	46.70	1.09	0.97
85	18	5.13	15.57	15.17	1.06	42.21	41.14	0.96	1.10
86	22	5.04	15.30	15.19	1.06	43.39	43.14	1.01	1.05
87	20	4.30	13.12	15.26	1.07	38.44	44.70	1.04	1.03
88	22	4.46	13.76	15.42	1.08	40.71	45.64	1.07	1.01
89	19	4.95	15.29	15.44	1.08	44.10	44.55	1.04	1.04
90	25	4.51	13.94	15.45	1.08	38.69	42.90	1.00	1.08
91	18	4.77	14.78	15.49	1.08	39.45	41.35	0.97	1.11
92	21	4.58	14.20	15.50	1.08	41.41	45.21	1.06	1.02
93	18	4.88	15.14	15.51	1.09	39.34	40.31	0.94	1.16
94	23	4.62	14.43	15.62	1.09	42.54	46.04	1.08	1.01
95	19	4.63	14.77	15.95	1.12	41.54	44.86	1.05	1.07
96	20	4.19	13.39	15.97	1.12	39.80	47.50	1.11	1.01
97	23	4.37	13.99	16.01	1.12	40.36	46.17	1.08	1.04
98	19	5.13	16.49	16.07	1.12	45.33	44.18	1.03	1.09
99	22	4.49	14.46	16.10	1.13	41.34	46.03	1.08	1.05
100	19	4.37	14.17	16.22	1.13	40.09	45.77	1.07	1.06
Aver.	22	4.80	13.69	14.29	1.00	41.04	42.87	1.00	1.00
Average of those 18 years of age (12 subjects)	18	4.84	14.11	14.59	1.02	41.16	42.60	1.00	1.02
Average of those 19 to 30 years of age (88 subjects)	22.4	4.79	13.64	14.25	1.00	41.02	42.90	1.00	1.00
Average for men 19 to 30 years of age [4]	24.5	5.39	15.76	14.66	1.00	44.84	40.80	1.00	1.00

It is equally important, however, to know the actual frequency distribution of the counts. The frequency distribution of our counts is shown in figure 2. Note that about 90 per cent of the counts fall between 4.3 and 5.3 million. The average is indicated in the chart (as also in charts 3 to 7) by a column having oblique lines in its lower portion. It will be noticed that the average count is also the most frequently occurring count. The detailed results are given in the table.

Our average red cell count of 4.8 million is distinctly higher than that given for women in most texts. It is lower by 0.6 million than the average count (5.4 million) reported for males in our previous article.[4]

HEMOGLOBIN CONTENT OF THE BLOOD IN NORMAL WOMEN

Only a few estimations for hemoglobin which are reported in the literature are sufficiently accurate to be of value. We could find reliable estimations on only sixty-four women between the ages of 18 and 30 years; they are as follows:

Williamson[14] (spectrophotometer): 49 women, averaging 15.11 Gm. per one hundred cubic centimeters.
Gram and Norgaard[6] (Autenrieth-Konigsburger colorimeter method): 6 women, averaging 12.82 Gm.
Haden[7] (Van Slyke's method): 9 women, averaging 13.5 Gm.
Total: 64 women, averaging 14.67 Gm. per one hundred cubic centimeters.

The wide variations between the averages reported by different authors are undoubtedly due to the small number of cases examined by each.

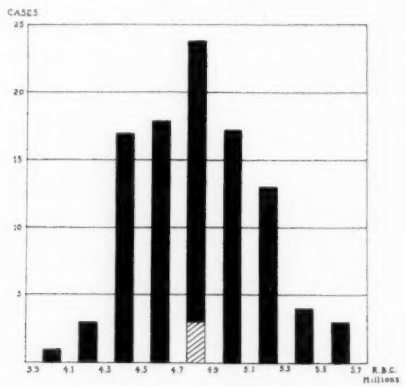

Fig. 2.—Red cell counts in one hundred healthy young women.

In addition, we have found reports of 143 examinations of women in which the age was not stated, or in which the methods used were of doubtful accuracy. They are distributed as follows:

Lundsgaard[15] (Palmer's method): 1 woman, averaging 13.04 Gm.
Bie and Möller[8] (Meissling colorimeter): 10 women, averaging 13.3 Gm.
Bing[9] (Sahli method): 51 women, averaging 13.87 Gm.
Leichtenstern[16] (spectrophotometer): 13 women, averaging 13.49 Gm.

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14. Williamson, C. S.: Influence of Age and Sex on Hemoglobin, Arch. Int. Med. **18**:505 (Oct.) 1916.

15. Lundsgaard, C.: Studies of Oxygen in the Venous Blood, J. Biol. Chem. **33**:133 (Jan.) 1918.

16. Leichtenstern, O.: Untersuchungen über den Haemoglobingehalt des Blutes in gesunden und kranken Zuständen, Leipzig, 1878. All of these subjects were between 18 and 30 years of age.

Gram[10] (Autenrieth Hellige colorimeter): 56 women, averaging 11.87 Gm.
Haldane[17] (Haldane oxygen capacity method): 12 women, averaging 12.31 Gm.
Total: 143 women, averaging 12.88 Gm.

The results have all been calculated as grams of hemoglobin per one hundred cubic centimeters of blood because so many different figures are used as 100 per cent hemoglobin by manufacturers of hemoglobinometers (thus making the percentage figure almost meaningless). Many results reported in the literature had to be discarded because the authors failed to state the method used. As Haskins and Osgood[18] have recently shown, many of the hemoglobin methods in common use are extremely inaccurate;[19] therefore, until accurate methods are universally used, every one reporting hemoglobin figures should state the method of estimation. Much confusion will be avoided if these results are always reported as grams per one hundred cubic centimeters.

By the Osgood-Haskins[20] method (the maximum error not being over 2 per cent) our average on 100 women between 18 and 30 years of age was 13.69 grams per one hundred cubic centimeters of blood. It will be seen from figure 3 that the average is also the most frequently occurring result, and that about 90 per cent of the results fall between 12 and 15.5 Gm. Our lowest estimation was 10.98 Gm., and the highest 16.49 Gm.

COLOR INDEX

The essentials for a color index determination that will be of value in diagnosis are: (1) an accurate red cell count on the patient's blood, (2) an accurate hemoglobin estimation on the same blood and (3) a normal standard for comparison. This standard is the average hemoglobin coefficient in healthy persons of the same sex and in the same age group. We have previously[4] defined the term *hemoglobin coefficient* as

17. Haldane, J.: The Colorimetric Determination of Hemoglobin, J. Physiol. **26**:497 (June) 1901. Five of these subjects were between 18 and 30 years of age.

18. Haskins, H. D., and Osgood, E. E.: Methods of Estimating Hemoglobin, Northwest Med. **25**:500 (Sept.) 1926.

19. It is worthy of note that at least three of the young women included in this series had been told by reputable physicians that they had chlorosis because the hemoglobin estimation by the Dare method was around 65 per cent. In each case estimation by an accurate method showed over 12.4 Gm. hemoglobin per one hundred cubic centimeters (90 per cent), and the color index was well within the normal range. On the other hand, three cases of definite chlorosis (not included in this series) with color indexes of 0.82, 0.68 and 0.67, respectively, were found which had been overlooked by other methods although the pallor was so marked in each case that we suspected the diagnosis at the time the blood was taken.

20. Osgood, E. E., and Haskins, H. D.: A New Permanent Standard for Estimation of Hemoglobin by the Acid Hematin Method, J. Biol. Chem. **57**:107 (Aug.) 1923.

"the number of grams of hemoglobin per hundred cubic centimeters of blood calculated to a red cell count of 5 million per cubic millimeter," and we use it with this meaning. The color index is calculated by dividing the percentage of hemoglobin by the percentage of red cells. For this calculation the normal hemoglobin coefficient (for the patient's age and sex) is considered as 100 per cent, and a red cell count of 5 million is considered as 100 per cent.

We were able to find in the literature satisfactory data for calculating hemoglobin coefficients reported for only fifteen women between 18 and 30 years of age. The results follow:

Gram and Norgaard[6]: 6 women, averaging 14 Gm.
Haden[7]: 9 women, averaging 15.7 Gm.
Total: 15 women, averaging 15 Gm.

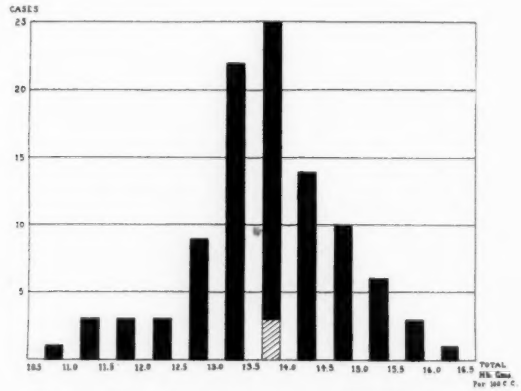

Fig. 3.—Total hemoglobin in one hundred women.

This number of cases is obviously too small to be of much value in determining the actual average. Our average on 100 women was 14.29 Gm. As the second decimal is not significant, we recommend 14.3 Gm. as the normal hemoglobin coefficient in women and have used it as 100 per cent hemoglobin in calculating color indexes. The range of distribution is shown in frequency figure 4. The tendency to a double peak is too slight to be statistically significant. If a larger number of cases were examined, the average would undoubtedly be the most frequently occurring figure. About 90 per cent of the results fall between 13 and 16 Gm., corresponding to color indexes between 0.9 and 1.10. The lowest color index was 0.83 and the highest was 1.13.

TOTAL CELL VOLUME

Estimations of cell volume in women measured by our technic[4] have not as yet, been reported. Gram and Norgaard,[6] using a slightly dif-

ferent but equally accurate method, have reported estimations on six women (18 to 30 years old) averaging 40.4 cc., and by a less satisfactory method Haden [7] has reported estimations on nine women (18 to 30) averaging 39.7 cc. of packed cells per one hundred cubic centimeters of blood. In addition Gram [21] reports an average of 41 cc., with extremes of 37 and 45 cc. on twenty-five normal women (ages and red cell counts not stated). These results agree well with our average of 41 cc. on 100 women. Figure 5 shows that this average is also the most frequently occurring figure, and that over 90 per cent of the results fall between 37 and 45 cc. The extremes were 35.29 cc. and 46.33 cc.

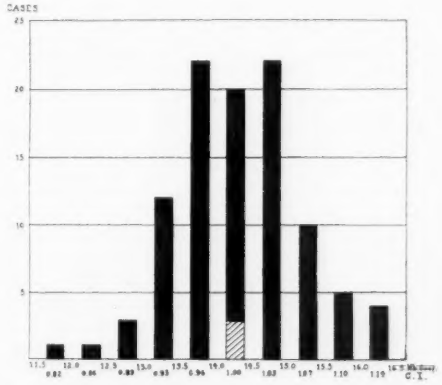

Fig. 4.—Hemoglobin coefficients and color indexes in one hundred women.

THE VOLUME INDEX

Since a high volume index is the most valuable and the most constant single laboratory finding in pernicious anemia, the importance of its accurate determination cannot be overemphasized. This index expresses the ratio between the average size of the red cells in the blood examined and the average size of the red cells in the blood of healthy persons of the same sex and in the same age group. It is determined by dividing the volume of cells, expressed in per cent (the average normal volume coefficient for the patient's age and sex being taken as 100 per cent), by the percentage of red cells (5 million being 100 per cent). We have previously [4] defined the term *volume coefficient* as "the volume of packed red cells per hundred cubic centimeters of blood calculated to a red cell count of 5 million."

Gram and Norgaard [6] report the only satisfactory volume coefficients we were able to find in the literature, but they examined only six women

21. Gram, H. C.: A New Method for the Determination of the Fibrin Percentage in Blood and Plasma, J. Biol. Chem. **49**:279 (Dec.) 1921.

in this age group. Their average of 44 becomes 42.5 when 3.5 per cent is deducted [22] for the difference in technic, and this agrees well with our average of 42.8. We also mention Haden's [7] results on nine women (18 to 30 years of age), although we believe his average (46.2) is too high. He neglected to centrifugalize to constant volume, and our experience has shown that his thirty minute period of centrifugalizing at 2,500 revolutions a minute is not sufficient to pack completely the cells of many normal specimens of blood. Sedimentation times of normal specimens of blood vary markedly, and some are high. Therefore, if actual cell volume is to be determined, we cannot overemphasize the importance of centrifugalizing until the cell volume remains constant.

We must repeat our warning that the average of a small number of cases should never be taken as a standard. For instance, the first twenty-five cases of our series gave a volume coefficient (43.68) higher

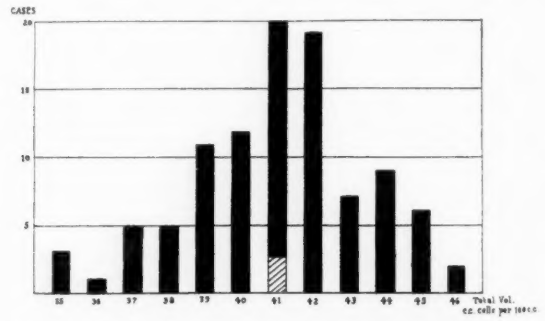

Fig. 5.—Total volume of cells in one hundred women.

than the average for the 100 cases by 2 per cent. Blood standards should not be based on a series of less than 100 cases.

Our average volume coefficient on 100 women was 42.8 cc., which is significantly higher than the average figure (40.8 cc.) found previously on young men.[4] This result was unexpected, and we have been unable to find any reason why young women should have larger cells than young men. The difference is about seven times the probable error of determination; so it is unlikely that it is due to random sampling as might be the case if only a small number of cases were examined. The technic used in the two series was identical in every detail, including the use of the same centrifuge and centrifuge tube. Several of the estimations on women were interspersed between the estimations on men; hence a variation in technic is improbable. This apparent difference should be confirmed by other workers on a large series of subjects.

22. The justification for this deduction has already been discussed in a previous article (footnote 4).

Reference to figure 6 shows that the extremes are 36.96 and 47.5, and that the average as well as the range of the most frequently occurring results (38.8 to 46.8) is higher than the corresponding figures for men. As the difference of five cases between the peak and the average is less than twice the probable error of the frequency, the peak of the curve would probably occur at the average in a larger series of cases. Over

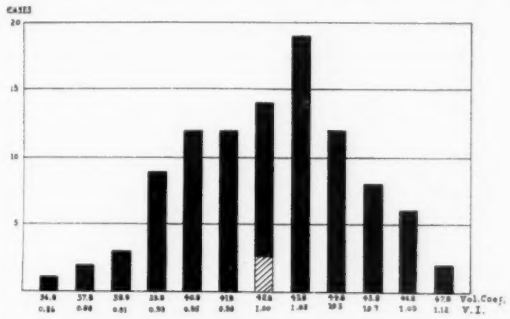

Fig. 6.—Volume coefficients and volume indexes in one hundred women.

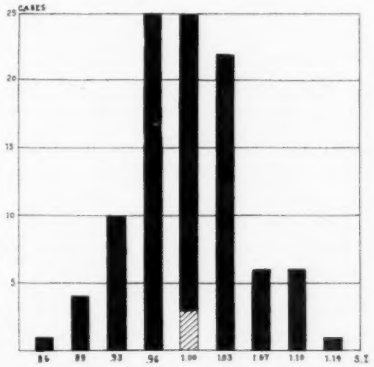

Fig. 7.—Saturation indexes in one hundred women.

90 per cent of the results correspond to volume indexes between 0.9 and 1.1. The lowest volume index was 0.86 and the highest was 1.11.

SATURATION INDEX

Haden[7] coined the term saturation index for the figure expressing the ratio between the concentration of hemoglobin per unit volume of cells in a particular subject and the average concentration of hemoglobin per unit volume of cells in normal subjects of the same sex and age group. It is most easily calculated by dividing the color index by the volume index.

Its clinical significance has not been fully worked out as yet. Our incomplete unpublished work shows that it is always low in anemia caused by chronic hemorrhage, either alone or complicating other types of anemia, and that it is within the normal range in pernicious anemia, aplastic anemia, hemolytic anemia and anemia caused by acute hemorrhage. The saturation index figure is probably never high.

Chart 7 shows that over 90 per cent of the results fall between 0.9 and 1.1. Fifty-six per cent of the women gave saturation indexes close to the average, that is, between 0.97 and 1.03. The extremes were 0.87 and 1.16.

METHOD OF CALCULATING RESULTS

It seems to us of value to give an illustration of our method of calculating results. For instance, in case number 100 our experimental data were as follows: 4.37 million red cells, 102.7 per cent hemoglobin and 1.58 cc. of packed red cells in our special centrifuge tube from 3.95 cc. of whole blood.

Calculations:

Total hemoglobin $= (102.7 \times 13.8) \div 100 = 14.17$ Gm. per 100 cc.

The factor 13.8 is used because we adopted for our hemoglobin method the same standard figure as is used for the Van Slyke, the Dare, and most other hemoglobin methods (100 per cent meaning a content of 13.8 Gm. per 100 cc.)

Hemoglobin coefficient $= 14.17 \times (5.00 \div 4.37) = 16.22$ Gm.

Color index = per cent Hb. ÷ per cent red cells.

$$\text{Per cent Hb.} = \frac{14.17 \times 100}{14.3} = 99.2 \text{ per cent.}$$

The figure 14.3 is the average hemoglobin coefficient.

$$\text{Per cent cells} = \frac{4.37 \times 100}{5.00} = 87.4 \text{ per cent.}$$

$$\text{Therefore, the color index} = \frac{99.2}{87.4} = 1.13.$$

Total volume of cells $= (1.58 \div 3.95) \times 100 = 40$ cc.

Volume coefficient $= (40 \times 5) \div 4.37 = 45.77$ cc.

Volume index = cell volume per cent ÷ per cent red cells.

Cell volume per cent $= (40 \times 100) \div 42.8 = 93.5$ per cent.

The figure 42.8 is the average volume coefficient.

$$\text{Volume index} = \frac{93.5}{87.4} = 1.07.$$

$$\text{Saturation index} = \text{color index} \div \text{volume index} = \frac{1.13}{1.07} = 1.06.$$

For regular routine work the hemoglobin and volume coefficient would not be calculated. A set of tables which will greatly simplify the calculations is being prepared by one of us and will be published soon in the *Journal of Laboratory and Clinical Medicine.*

SUMMARY

1. The figures usually given for normal red cell counts in men (5 million) and in women (4.5 million) are incorrect. They never had a sound experimental basis.

2. The actual average red cell count in 100 women from 18 to 30 years of age was 4.8 million, 90 per cent of the cases falling between 4.3 and 5.3 million. In contrast to this, our previous work [4] showed an average count of 5.4 million in 137 men (19 to 30 years of age) with 90 per cent falling between 4.7 and 6.1 million.

3. The average total hemoglobin per one hundred cubic centimeters of blood in young women is 13.7 Gm. with 90 per cent of the results falling between 12 and 15.5 Gm. In men the average was 15.8 Gm. (not 13.8 Gm. as is commonly stated), and 90 per cent of the results fell between 14 and 18 Gm.

4. The average *hemoglobin coefficient* [23] in young women is 14.3 Gm. and in men 14.7 Gm. These are the figures that should be taken as 100 per cent hemoglobin in calculating color indexes of young adults.

5. The total volume of packed red cells per one hundred cubic centimeters of blood averages 41 cc. in women (90 per cent between 37 and 45) and 45 cc. in men (90 per cent between 40 and 50).

6. The average *volume coefficient* [23] in women is 42.8 cc., and in men is 41 cc. provided that our technic [4] is used. These are the figures that should be used as 100 per cent in calculating volume indexes. We cannot account for the slightly larger red cells in women, but the difference appears to be significant.

7. The various indexes (color, volume and saturation) will average 1.0 in normal young adults if they are properly calculated and are based on accurate estimations of cells, hemoglobin and cell volume. About 90 per cent of the results will fall between 0.9 and 1.1.

One must be cautious in interpreting results between 0.8 and 0.9 and between 1.1 and 1.2, because a few normal persons (up to 10 per cent) give indexes in these ranges in spite of careful technic and accurate methods. In all of our cases, of both men and women, we found only six indexes outside the range 0.85 to 1.15.

8. The standards proposed on the basis of our work (100 female and 137 male subjects) should be used by physicians until more extensive investigations are reported.

9. The literature relating to these observations in women has been reviewed, but it is unsatisfactory because complete data comparable to our own are given for only fifteen women from 18 to 30 years of age.

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23. The terms hemoglobin coefficient and volume coefficient were suggested by us in a previous article (footnote 4).

METABOLIC STUDIES IN THE TREATMENT OF POLYCYTHEMIA VERA WITH PHENYLHYDRAZINE *

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Phenylhydrazine hydrochloride was used for the first time in the treatment of polycythemia vera in 1918 by Eppinger and Kloss.[1] They used the drug in four cases in which the number of erythrocytes was satisfactorily reduced, and the symptoms were relieved without apparent injurious effects on the patient. Others [2] on the continent have since reported their experiences. Owen [3] was the first in this country to record experience with this method, and he has more recently [4] amplified his previous report. Long,[5] and Brown and Giffin [6] have also attested its value.

So far as I know, quantitative metabolic studies have not been reported on patients with polycythemia vera during treatment with phenylhydrazine hydrochloride. Such studies not only should have academic interest, but should also furnish data by which the results of the treatment could be estimated.

The formula for phenylhydrazine is $C_6H_5NH—NH_2$. The drug and its compounds have been used extensively in the experimental production of anemia and in studying phases of hepatic injury. In 1885, Hoppe-Seyler [7] first employed the hydrochloride derivative in animal experimentation. He noted its blood-destroying qualities, which apparently were brought about by the reducing action of the drug on the hemoglobin. Acetyl phenylhydrazine was introduced into therapeutics

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* Abridgment of thesis submitted to the Factulty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Medicine, 1926.

1. Eppinger, H., and Kloss, K.: Zur Therapie der Polyzythämie, Therap. Monatsh. **32**:322, 1918.

2. Strasburger, J.: Zur Behandlung der Polyzythämie, Therap. Monatsh. **35**:777, 1921. Taschenberg, E. W.: Ueber die Behandlung der Polyzythämie mit Phenylhydrazin, Deutsche med. Wchnschr. **2**:774, 1921.

3. Owen, Trevor: A Case of Polycythaemia Vera with Special Reference to the Familial Features and Treatment with Phenylhydrazin, Bull. Johns Hopkins Hosp. **35**:258, 1924.

4. Owen, Trevor: The Treatment of Erythremia with Phenylhydrazin, J. A. M. A. **85**:2027 (Dec. 26) 1925.

5. Long, P. H.: Effect of Phenylhydrazin Derivatives in the Treatment of Polycythemia, J. Clin. Investigation **4**:315, 1926.

6. Brown, G. E., and Giffin, H. Z.: Studies on Polycythemia Vera (Erythremia) During Treatment with Phenylhydrazin, Arch. Int. Med. **38**: 321 (Sept.) 1926.

7. Hoppe-Seyler, Georg: Ueber die Wirkung des Phenylhydrazins auf den Organismus, Ztschr. f. physiol. Chem. **9**:34, 1885.

because of its antipyretic properties (hence the name pyrodine), but was soon abandoned when its hemolytic action was noted. In a case recorded by Renvers [8] there was a fall in erythrocytes from 4,000,000 to 2,800,000 in three days, with the administration of 0.5 Gm. of the drug. The hemolytic action was confirmed by Fränkel,[9] among others, who made a study on two dogs in which a fixed diet was used. He noted an increased excretion of nitrogen after subcutaneous injections of acetyl phenylhydrazine. He believed that this increased excretion of nitrogen was due to protoplasmic injury and to the decreased oxidation occurring in consequence of the destruction of blood.

Fränkel, and later Tallquist,[10] noted the frequency of hepatic injury in pyrodine anemia. This occurs in the poisoning produced by hydrazine compounds generally, as shown by Wells,[11] although not to the same degree in all compounds, as shown by Bodansky.[12] The latter, while studying the hepatic injury produced by different hydrazine compounds, found extensive degeneration of the liver, marked hyperpigmentation of the spleen and extreme destruction of the red corpuscles in one dog following subcutaneous injections of phenylhydrazine hydrochloride. In another animal injections of acetyl phenylhydrazine produced marked anemia, but little destructive change could be demonstrated in the hepatic cells.

Von Roeder, quoted by Kühnau,[13] found a marked increase in the leukocytes in rabbits receiving intraperitoneal injections of phenylhydrazine hydrochloride. Tallquist also observed this in his animals with pyrodine poisoning, the increase affecting chiefly the myeloblastic elements. He also found in a subsequent investigation on the same animal that larger and larger doses of the drug were needed to produce similar degrees of anemia. Morawitz and Pratt [14] ascribed this occurrence to increased resistance of the erythrocytes to hemolytic agents generally brought about as the response of the body to the toxic action of the drug.

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8. Renvers: Ueber Pyrodin, Deutsche med. Wchnschr. **15**:964, 1889.

9. Fränkel, A.: Ueber das Verhalten des Stoffwechsels bei Pyrodinervergiftung, Ztschr. f. klin. Med. Supplement **17**:239, 1890.

10. Tallquist, F. W.: Ueber experimentelle Blutgriff-Anämien, Berlin, Hirschwald, 1900, pp. 205.

11. Wells, H. G.: The Pathological Anatomy of Hydrazine Poisoning, J. Exper. Med. **10**:457, 1908.

12. Bodansky, Meyer: The Action of Hydrazin and Some of Its Derivatives in Producing Liver Injury as Measured by the Effect on Levulose Tolerance, J. Biol. Chem. **58**:799, 1923-1924.

13. Kühnau: Ueber das Verhalten des Stoffwechsels und der weissen Blutelemente bei Blutdissolution, Deutsches Arch. f. klin. Med. **58**:339, 1897.

14. Morawitz, P., and Pratt, J.: Einige Beobachtungen bei experimentellen Anämien, München med. Wchnschr. **2**:1817, 1908.

Samuely [15] reported the results of carefully conducted quantitative metabolic studies in experimental anemia using acetyl phenylhydrazine as one of his hemolytic agents. His data showed, among other things, a decline in the excretion of urea nitrogen from 84 to 71 per cent, while the excretion of ammonia increased correspondingly.

The available data [16] on the nitrogenous metabolism in cases of polycythemia vera in which a fixed diet was used indicate little change from the normal. There is an increase of uric acid of the whole blood which Isaacs [17] has attributed to an increase in the extruded nuclear material associated with increased formation of erythrocytes. There is usually an increase in the amino-acid content of the blood. Numerous workers have reported the occurrence of an increased basal metabolic rate, the increase seeming to be somewhat proportional to the erythrocytic content of the blood, although this is not always the case.

MATERIAL STUDIED AND METHODS EMPLOYED

This report embodies studies of the chemistry of blood and urine in four cases of polycythemia vera in which a reduction in erythrocytes and blood volume was affected by phenylhydrazine hydrochloride. A weighed diet or standard food portion was given each patient, the food values of which were computed from Atwater and Bryant's [18] tables. Unless otherwise stated, this diet daily consisted of 40 Gm. of protein, 55 Gm. of fat and 200 Gm. of carbohydrate with a caloric value of 1,500, and may be considered a basal maintenance diet for the average adult patient at rest. The relatively low content of protein was prompted by the possibility of renal and hepatic injury being produced by the phenylhydrazine hydrochloride. The total twenty-four hour quantity of urine was saved, and toluene was added as a preservative. Attempts were made to secure uniform times of collecting the specimens, and for the most part this was accomplished. Blood for study was drawn by venipuncture from the median basilic vein at regular intervals before breakfast.

The following methods were used in the study of the urine: for total nitrogen, the Kjeldahl method; for urea nitrogen, the urease method; for ammonia nitrogen, the Folin and Bell method; for creatine, creatinine

15. Samuely, Franz: Stoffwechseluntersuchungen bei experimenteller Anämie, Deutsches Arch. f. klin. Med. **89**:220, 1906.

16. Gordon, J. M.: Zur Kenntniss der Erythräm, Ztschr. f. klin. med. **68**:1, 1909. Löw, Josef, and Popper, Hugo: Beitrag zur Klinik der Polyzythämie, Wien. klin. Wchnschr. **21**:357, 1908. Senator, H.: Ueber Erythrozytosis (Polycythaemia rubra) Megalosplenica, Ztschr. f. klin. med. **60**:357, 1909.

17. Isaacs, Rafael: Pathologic Physiology of Polycythemia Vera, Arch. Int. Med. **31**:289 (Feb.) 1923.

18. Atwater, W. O., and Bryant, A. P.: The Chemical Composition of American Food Materials, U. S. Department of Agriculture, Washington, Government Printing Office, 1906, Bull. 28.

and uric acid, the Folin method. In the study of the blood, the methods used were: the acid-hematin method of Haden for hemoglobin; Folin's methods for nonprotein nitrogen, creatinine, sugar, uric acid and amino-acids; the urease method for urea; van den Bergh's method for serum bilirubin; Van Slyke's method for carbon dioxide combining power; and Keith, Rowntree and Geraghty's dye method for blood volume. The fecal nitrogen was not determined; the total nitrogen was computed by adding 10 per cent of the food nitrogen to the urinary nitrogen.

Phenylhydrazine hydrochloride was given by mouth in an average dosage of 0.3 Gm. daily. This dose was continued until the desired therapeutic effect had been obtained or had been approached, so that there was considerable variation in the total amount given in the different cases. The nitrogen content of the drug is too small to affect the general result.

The changes observed in the four cases studied are given in the tables accompanying the case reports. The daily changes are shown in the illustrations. In the tables the urinary changes are reported in terms of the daily average over a five day period. These cases are among those recently reported in a detailed clinical study by Brown and Giffin.[6] Complete studies could not be made in case 1 (Brown and Giffin, case 2), but I report the data obtained on four representative days during the course of treatment. In case 2 (Brown and Giffin, case 7) it was not possible to make studies before the administration of phenylhydrazine was started, but in case 4 (Brown and Giffin, case 4) a two day and in case 3 (Brown and Giffin, case 3) a five day control period was arranged.

REPORT OF CASES

CASE 1.—The results of examination of the blood in a man, aged 56, were: hemoglobin content, 29.4 Gm. per hundred cubic centimeters of blood; erythrocytes, 8,530,000; relative viscosity, 12; total blood volume, 12,400 cc. or 190 cc. for each kilogram of body weight. The hematocrit revealed 72 per cent of erythrocytes. The spleen was palpable. The patient was given 6.4 Gm. of phenylhydrazine over a period of sixteen days. Destruction of blood was marked, the hemoglobin being reduced to 9.5 Gm. and the erythrocytes to 2,180,000, while the blood volume was reduced to 5,050 cc. (table 1).

CASE 2.—The condition of a man, aged 58, was diagnosed polycythemia vera, although the erythrocytes numbered only 5,490,000. There was 19 Gm. of hemoglobin per hundred cubic centimeters of blood; the total blood volume was 8,350 cc. or 112 cc. for each kilogram of body weight, and the relative viscosity of the whole blood was 10.5. The volume of erythrocytes was 50 per cent by hematocrit examination. The spleen was palpable. A total dose of 4.5 Gm. was given over a period of fifteen days. The hemoglobin was reduced to 6.5 Gm. per cent, the erythrocytes to 2,020,000 and the total blood volume to 6,150 cc. Five days elapsed after the phenylhydrazine was started before the study of the nitrogen partitions of the urine was begun (table 2 and chart 1).

CASE 3.—A man, aged 43, had an erythrocyte count of 8,750,000 on admission to the hospital. The hemoglobin content was 27.4 Gm. per hundred cubic centimeters of blood, and the whole blood volume was 13,350 cc. The relative

TABLE 1.—*The Effect of Phenylhydrazine on the Urine and Blood in a Case of Polycythemia Vera*

(Patient a man, aged 56)

| Date, 1925 | Weight, Kg. | Diet, Gm. | | | Urine | | | | | | | | | | | Blood | | | | | | | | | | |

TABLE 2.—*The Effect of Phenylhydrazine on the Urine and Blood in a Case of Polycythemia Vera*

(Patient a man, aged 58)

Date, 1925	Weight, Kg.	Diet, Gm.			Urine								Blood															
		Protein	Fat	Carbohydrate	Total Nitrogen, Gm.	Urea and Ammonia Nitrogen, Gm.	Creatinine Nitrogen, Gm.	Creatine Nitrogen, Gm.	Uric Acid Nitrogen, Gm.	Rest Nitrogen, Gm.	Nitrogen Balance, Gm.	Phenolsulphonephthalein, per Cent Return in Two Hours	Blood Volume, Cc.	Erythrocytes, Millions	Hemoglobin, Gm. per 100 Cc.	Hematocrit, per Cent	Nonprotein Nitrogen, Mg.	Urea Nitrogen, Mg.	Creatinine Nitrogen, Mg.	Uric Acid Nitrogen, Mg.	Amino-Acid Nitrogen, Mg.	Serum Bilirubin, Mg.	Van den Bergh Direct Reaction	Phenol-tetrachlorphthalein in Serum, per Cent: Fifteen Minutes	Phenol-tetrachlorphthalein in Serum, per Cent: One Hour	Phenol-tetrachlorphthalein in Serum, per Cent: Two Hours	Carbon Dioxide Combining Power, per Cent by Volume	Basal Metabolic Rate: Du Bois Standard, per Cent	Phenylhydrazine, Gm.
2/15	—	—	—	—	—	—	—	—	—	—	—	50	8,350	5.49	19.0	58	40	19	0.74	0.90	14.3	1.7	0	—	—	—	—	—	1.2
2 20-2/24	73.4	40	55	200	12.00	11.00	0.63	0.04	0.25	0.00	— 6.24	60	—	6.01	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1.5
2/25-3/ 1	72.6	40	55	200	16.38	14.35	0.63	0.07	0.18	1.15	—10.66	—	—	4.09	16.0	—	—	22	0.48	1.00	9.3	3.7	0	—	—	—	—	—	1.5
3/ 2-3/ 6	72.3	40	55	200	15.98	14.87	0.67	0.07	0.29	—	—10.22	75	6,800	2.73	11.6	40	42	29	0.48	0.93	8.3	4.8	0	5	1	0	—	—	0.3
3/ 7-3/11	73.1	40	55	200	10.20	8.00	0.63	0.04	0.22	1.03	— 4.42	—	6,150	2.02	6.5	23	31	16	0.74	—	7.7	3.0	0	—	—	—	59	+14	0
3/12-3/16	73.3	40	55	200	8.02	—	—	—	—	—	— 0.53	—	6,150	2.26	8.3	24	31	8	0.56	1.00	7.7	1.4	0	—	—	—	53	+10	0

viscosity was 11.8. The spleen was enlarged, extending 13 cm. below the costal margin. The diagnosis was polycythemia vera. The patient received 6.1 Gm. of phenylhydrazine hydrochloride during a period of sixteen days. A marked decrease in the circulating blood volume in the hemoglobin and in the number of erythrocytes occurred. Marked icterus was seen at the height of erythrocytic destruction, and hemoglobinuria was demonstrated. The excretion of phenolsulphonphthalein decreased to 25 per cent in two hours, but later returned to normal (table 3, chart 2).

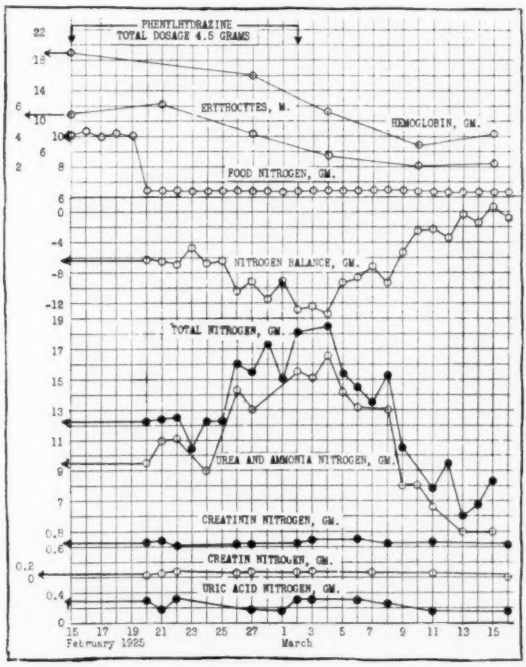

Chart 1.—Effect of phenylhydrazine on the blood and the nitrogenous partition products in the urine in a case of polycythemia vera.

Case 4.—In a woman, aged 31, the erythrocytes numbered 6,890,000, the hemoglobin content was 23.3 Gm. per hundred cubic centimeters of blood, and the whole blood volume was 7,700 cc. or 167 cc. for each kilogram of body weight. The spleen extended 4 cm. below the costal margin. A total dose of 3.5 Gm. of phenylhydrazine was given during a period of eleven days. The reduction in hemoglobin and erythrocytes and blood volume was definite. On one occasion, during the time of apparent maximal destruction of erythrocytes, the patient vomited blood-streaked material. The urine contained macroscopic blood, and slight jaundice developed. Moderate albuminuria was also present (table 4 and chart 3).

TABLE 3.—*The Effect of Phenylhydrazine on the Urine and Blood in a Case of Polycythemia Vera*

(Patient a man, aged 43)

| | | | Diet, Gm. | | | Urine | | | | | | | | | | | Blood | | | | | | | | | | |

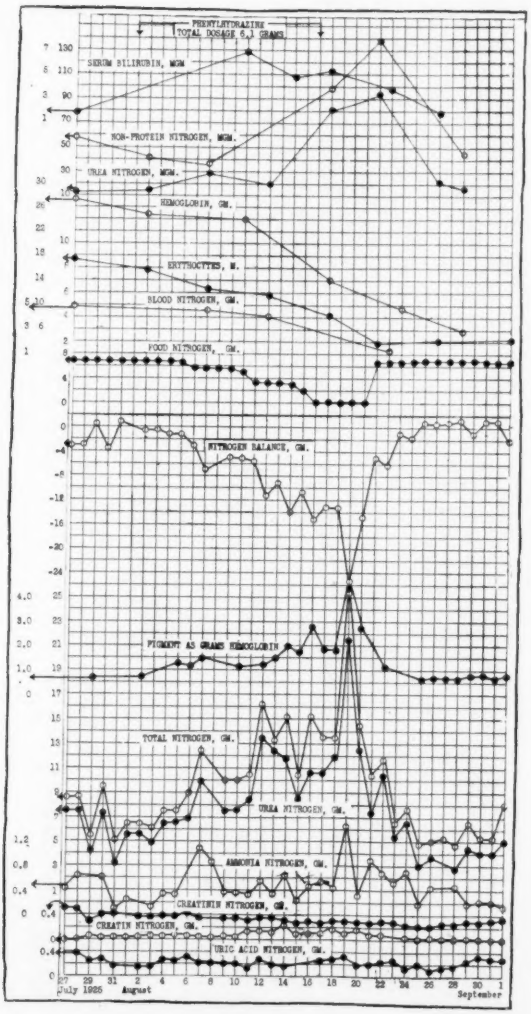

Chart 2.—Effect of phenylhydrazine on the blood and the nitrogenous partition products in the urine in a case of polycythemia vera.

TABLE 4.—*The Effect of Phenylhydrazine on the Urine and Blood in a Case of Polycythemia Vera*

(Patient a woman, aged 31)

Date, 1925	Weight, Kg.	Diet, Gm.			Urine									Blood																
		Protein	Fat	Carbohydrate	Total Nitrogen, Gm.	Urea Nitrogen, Gm.	Ammonia Nitrogen, Gm.	Creatinine Nitrogen, Gm.	Creatine Nitrogen, Gm.	Uric Acid Nitrogen, Gm.	Rest Nitrogen, Gm.	Nitrogen Balance, Gm.	Phenolsulphonephthalein, per Cent Return in Two Hours	Blood Volume, Cc.	Erythrocytes, Millions	Hemoglobin, Gm. per 100 Cc.	Hematocrit, per Cent	Nonprotein Nitrogen, Mg.	Urea Nitrogen, Mg.	Creatinine Nitrogen, Mg.	Uric Acid Nitrogen, Mg.	Amino-Acid Nitrogen, Mg.	Serum Bilirubin, Mg.	Van den Bergh Direct Reaction	Phenol-tetrachlor-phthalein in Serum, per Cent			Blood Sugar, Mg.	Basal Metabolic Rate: Du Bois Standard, per Cent	Phenylhydrazine, Gm.
																									Fifteen Minutes	One Hour	Two Hours			
6/20-6/21	46.0	40	50	200	5.90	5.00	0.20	0.33	0.00	0.13	0.25	—0.14	50	7,700	6.89	23.3	71	15	5	0.44	1.13	11.0	1.5	0	12	5	0	105	+19	0
6/22-6/27	46.0	40	50	200	7.35	5.37	0.34	0.34	0.01	0.15	1.63	—1.59	40	—	—	—	—	—	—	—	—	—	—	—	—	—	—	66	+16	1.6
6/28-7/ 2	45.7	40	50	200	8.75	7.30	0.44	0.34	0.00	0.13	—	—2.99	—	7,830	5.82	24.0	62	44	11	0.54	1.13	10.0	5.3	0	—	—	—	—	+37	1.6
7/ 3-7/ 7	44.5	40	50	200	13.80	11.35	0.28	0.38	0.04	0.18	1.44	—8.04	—	4,800	5.60	12.2	37	51	32	0.48	1.05	—	7.5	0	10	6	2	84	+27	0.3
7/ 8-7/12	42.0	40	50	200	11.10	8.77	0.54	0.38	0.03	0.28	1.08	—5.34	65	4,400	4.20	8.7	23	34	17	0.41	0.97	—	3.9	0	—	—	—	—	—	0
7/13-7/16	45.3	40	50	200	5.70	4.35	0.33	0.39	0.00	0.15	0.54	—0.06	50	4,200	2.50	8.4	23	30	11	0.45	1.00	—	1.4	0	—	—	—	—	+15	0

RESULTS

Urinary Changes.—Usually about seven days elapse following the administration of phenylhydrazine before the evidences of blood destruction are manifest. At this time increased excretion of nitrogen is found, further increase being rapid and progressive as the treatment is continued. The excretion of nitrogen is maintained at a high level for a number of days after withdrawal of the drug and then rapidly declines

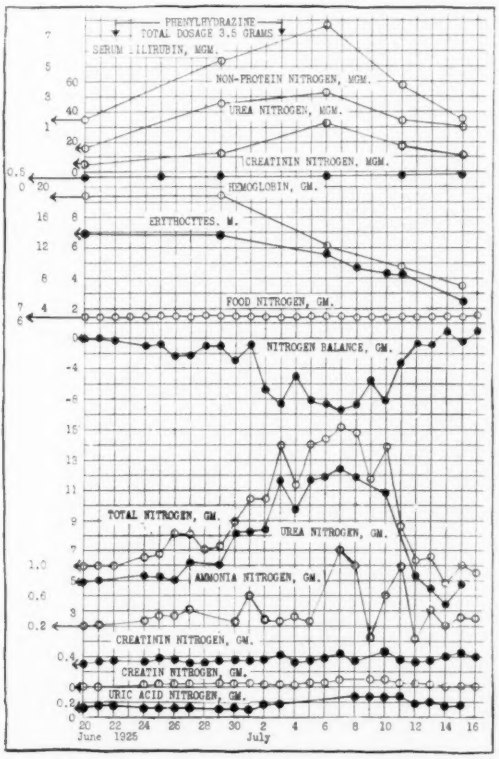

Chart 3.—Effect of phenylhydrazine on the blood and the nitrogenous partition products in the urine in a case of polycythemia vera.

to the initial level. The increase in nitrogen output is most marked during the period of greatest decrease in erythrocyte and hemoglobin content of the blood.

In case 3 the total nitrogen increased from a daily level of 7.47 to 25 Gm. After the drug was withdrawn, there was a continued daily negative nitrogen balance for several days; then the urinary nitrogen declined to 5.3 Gm. which, compared to the initial level of 7.47 Gm., indi-

cated slight nitrogen retention. During the time of maximal destruction of erythrocytes a daily negative nitrogen balance amounting to 12.15 Gm. or more occurred, and a total negative balance of 100 Gm. or more. A loss of weight occurred during the time of maximal destruction of erythrocytes, but this weight was rapidly regained after discontinuance of the drug. In all cases the estimated destruction of blood was more than sufficient to account for the negative nitrogen balance.

The urea nitrogen rose to a high level after the administration of phenylhydrazine. It gradually decreased to a normal level after the drug had been stopped. The variation in urea reflected accurately the variation in total nitrogen.

The excretion of ammonia showed variations which were for the most part within normal limits. On a few occasions values were obtained indicating excretion of ammonia amounting to 10 per cent of the total. However, the absence of significant fluctuations together with the relative constancy of the carbon dioxide capacity excluded any significant effect of the phenylhydrazine on the acid-base balance of the body.

In general, the creatinine showed little variation from normal values. If the creatinine which is eliminated is an index of destruction of living protoplasm, then such tissue is not involved in the protein destruction produced by the phenylhydrazine hydrochloride as used in these cases. In case 3 there was a slight relative decrease in the preformed creatinine excreted, although the total was unchanged. After nitrogen equilibrium had been reestablished subsequent to withdrawal of the drug, the total decreased to the level of the preformed creatinine.

Slight creatinuria was frequently present during the time of the administration of the phenylhydrazine hydrochloride. This rapidly disappeared after the drug was stopped. Cathcart [19] showed that the carbohydrate metabolism is concerned in some way with the conversion of creatine to creatinine. Greene, Connor [20] and I did not find evidence of a disturbance in the carbohydrate metabolism in these cases. Another and simpler explanation may be found in the fact that the erythrocyte contains practically all the circulating creatine.[21] In the disintegration of the corpuscle, creatine escapes in such amounts that small quantities appear in the urine.

Since the diet was not absolutely purin-free, the estimations of uric acid hold interest from their qualitative rather than from their quantitative value. For the most part the excretion of uric acid exhibited values within the normal range, from which the conclusion is made that

19. Cathcart, E. P.: Metabolism During Starvation, J. Physiol. **35**:500, 1907.

20. Greene, C. H., and Conner, H. M.: Diseases of the Liver: V. A Comparative Study of Tests for Hepatic Function in Certain Diseases of the Hematopoietic System. Arch. Int. Med. **38**:167 (Aug.) 1926.

21. Hunter, Andrew, and Campbell, W. R.: The Amount and the Distribution of Creatinine and Creatine in Normal Human Blood, J. Biol. Chem. **33**:169, 1918.

so far as the excretion of uric acid is an index of endogenous metabolism, this was not seriously deranged by the administration of phenylhydrazine.

The urine of patients taking phenylhydrazine is dark brown or mahogany. Hoppe-Seyler attributed this color to a pigment produced by the action of phenylhydrazine on hemoglobin. He showed its occurrence in vitro, but neither he nor subsequent investigators have been able to identify the supposed pigment with any of the usual hemoglobin derivatives. C. H. Greene quantitated this coloring matter, using an acid hematin solution as the standard. The results are shown in table 3 and chart 2 (case 3) in which the total pigment was calculated as grams of hemoglobin.

Changes in the Blood.—During the administration of phenylhydrazine hydrochloride, there was a decrease in the total nitrogen of the blood (table 3 and chart 2) paralleling the reduction in percentage of corpuscles in such cases. The decrease in the total nitrogen of the blood must be referred to the decrease in erythrocytes and directly related to this decreased hematocrit value, since there was not a marked change in the nitrogen content of the plasma and corpuscles when they were taken separately.

The nonprotein nitrogen and the urea showed definite increases which paralleled the amounts of these substances eliminated in the urine and returned to normal as the excess of nitrogen was excreted.

The blood urea showed the most marked increase of the nitrogenous contents and accounted well for the increased nonprotein nitrogen. Such increases were of moderate degree, except that in case 3 an increase in the urea nitrogen to 95 mg. occurred. At this time the excretion of phenolsulphonphthalein was decreased to 25 per cent in two hours. The response of the patient to eliminative procedures was prompt, and later tests indicated that permanent impairment of renal function had not occurred.

The creatinine nitrogen increased from 0.56 to 1.26 mg. in case 3, in which there were direct evidences of renal impairment. In the other cases studied evidence of gross departure from the initial values was not found.

The uric acid content of the blood did not change markedly from the initial levels. For the most part the values obtained were consistently in the upper limits of normal.

The amino-acid nitrogen of the blood is increased in cases of polycythemia. During the administration of phenylhydrazine, the amino-acid gradually fell to normal values.

The serum bilirubin content in cases of polycythemia vera is within normal limits. Shortly after the administration of phenylhydrazine was begun, bilirubinemia occurred, the maximal values of which were obtained at the time of apparent maximal destruction of erythrocytes.

Daily determinations of the serum bilirubin were not attempted, but there was a marked parallelism between the curves of serum bilirubin and nitrogen excreted in the urine. It is likely that the changes in the serum bilirubin precede somewhat the changes in the excretion of nitrogen, but definite evidence of this was not obtained.

As indicated in the reports of cases, clinical icterus developed during the course of the action of the drug. However, the van den Bergh reaction remained indirect during the time of the most marked changes. The reaction with the Gmelin test for bile in the urine did not demonstrate its presence.

Fructose Tolerance Test.—Bodansky has emphasized the changes in the fructose tolerance in dogs after toxic doses of phenylhydrazine and its derivatives. He considered the occurrence of hypoglycemia as indicative of the extent of hepatic injury. There was no change in the fasting blood sugar level in any of the cases studied, and the fructose tolerance did not change as a result of the administration of phenylhydrazine hydrochloride.

Phenoltetrachlorphthalein Test.—The results of the phenoltetrachlorphthalein test of Rowntree and Rosenthal were used in some of these cases as an index to possible hepatic injury. Negative results were obtained throughout.

Basal Metabolic Rate.—Characteristic changes were not observed in the heat exchange as indicated by the basal metabolic rate during the course of phenylhydrazine action. In cases 2 and 4 slight decreases were noted, but these were not considered significant. In general, it would appear that the heightened nitrogen catabolism did not significantly affect the transfer of energy.

COMMENT

The metabolic changes accompanying the therapeutic use of phenylhydrazine are as striking as the clinical effects. The origin of bile pigments from hemoglobin and the metabolic relationship between the destruction of hemoglobin and the formation of bilirubin are recognized. In the cases here reported this relationship is emphasized further by the appearance of a bilirubinemia which apparently corresponds roughly in degree with the intensity of the corpuscular destruction. The serum bilirubin can be used as a guide to the therapeutic action of the drug.

The bilirubinemia is of hemolytic origin and not due to obstruction, so that bilirubin does not appear in the urine, at least not in appreciable quantities. The urine, however, contains an unidentified brown pigment first described by Hoppe-Seyler, which apparently is a product of hemoglobin destruction. It appears in increasing amounts as the destruction of erythrocytes continues and disappears when the drug is with-

drawn. This pigment likewise can be demonstrated in the blood serum when the changes in the urine are most marked. Like Fränkel, I have been unable to demonstrate the presence of methemoglobin or hematin in the blood or urine. Neither have I been able to obtain positive tests for para-amino phenol, which Young [22] and others have demonstrated in cases of poisoning by aniline and acetanilid.

Urinalysis showed an increase in the urobilin and urobilinogen excreted during the period of drug action. The fate of the pigment moiety of the hemoglobin cannot be finally established in these experiments, since the excess bilirubin formed from destroyed erythrocytes would be excreted in the bile, and the latter could not be studied. The increase in the urobilin and urobilinogen in the urine furnishes further evidence, even though indirect, of the presence of such an excess of bile pigment in the intestine.

The changes in the urinary nitrogen apparently suffice to explain the fate of the protein moiety of the corpuscles and the hemoglobin molecule. The daily excretion of creatinine and uric acid in the urine did not change significantly during the period of administration of the drug. According to the current theories of protein metabolism, this would indicate an unchanged or normal total tissue metabolism. Boothby and his collaborators[23] have applied this hypothesis in explaining effects of the administration of thyroxin in producing catabolism of stored or deposited protein. Following the administration of phenylhydrazine to patients on a constant protein intake, there was a striking increase in the total nitrogen excreted in the urine. This increase can be explained almost wholly by an increase in the elimination of urea nitrogen. Fränkel considered that the increased excretion of nitrogen observed in animals after the administration of acetyl phenylhydrazine was evidence of general tissue injury. In view of the incomplete nature of his studies, this conclusion is not convincing. In the cases here reported the accompanying evidence of destruction of erythrocytes and the constant endogenous metabolism indicate that the increased excretion of urea depends on the destruction of the proteins of the corpuscles. The loss of nitrogen from the blood, whether calculated from the changes in the total blood volume or the total hemoglobin, was sufficient in all cases to account for all the excess of nitrogen appearing in the urine.

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22. Young, A. G.: Toxicological Studies of Anilin and Anilin Compounds. II. Hematological Studies of Anilin Poisoning, J. Pharmacol. & Exper. Therap. **27**:125, 1926. Young, A. G., and Wilson, J. A.: Toxicological and Hematological Studies of Acetanilid Poisoning, J. Pharmacol. & Exper. Therap. **27**:133, 1926.

23. Boothby, W. M.; Sandiford, Irene; Sandiford, Kathleen, and Slosse, Jean: The Effect of Thyroxin on the Respiratory and Nitrogenous Metabolism of Normal and Myxedematous Subjects. I. A Method of Studying the Reserve or Deposit Protein with a Preliminary Report of the Results Obtained, Tr. A. Am. Phys. **40**:195, 1925; Ergeber, d. Physiol. **24**:728, 1925.

Mild albuminuria, and later hemoglobinuria, followed by hematuria was observed in some of the cases. These changes have been recognized previously, and Fränkel describes similar effects from acetyl phenylhydrazine. He ascribed them primarily to the destruction of erythrocytes rather than to primary renal injury. In three of the cases of the present series there was no reduction in the phenolsulphonphthalein output or increase in the blood creatinine; however, there was a marked rise in the nonprotein nitrogen and urea content of the blood, which varied with the changes in the urinary nitrogen. It seems probable, as with the serum bilirubin, that the rise in the blood urea is due to hemoglobin catabolism at a rate in excess of the excretory power of the organism. In consequence there was a temporary flooding of the kidney with urea and retention of the excess which determined the changes in the blood stream. Similar although less marked changes have been reported in normal persons after a heavy meat meal or a high protein diet. Boothby and his collaborators also report a slight to moderate increase in the blood urea after the administration of thyroxin accompanying the mobilization of the deposit protein; the retention varied in different cases apparently according to the relative ability of the kidneys to eliminate as fast as the protein was deaminized.

The greater part of the retained urea is apparently the effect of renal flooding. A slight degree of primary renal injury cannot be excluded. In case 3, in which an excessive dose of the drug was used, temporary renal insufficiency was produced. The excretion of phenolsulphonphthalein decreased from 65 to 25 per cent, the blood creatinine nitrogen increased from 0.56 to 1.26 mg., and the blood urea nitrogen rose to 95 mg. The renal insufficiency was temporary, and normal function was quickly restored. Baker and Dodds [24] have recently emphasized the action of hemoglobin on the kidney. Such an effect may serve to explain the observed renal changes in view of the hemoglobinuria in this case.

The toxic action of hydrazine, phenylhydrazine and allied substances has been emphasized by all who have studied these compounds. Changes in the carbohydrate metabolism have been especially emphasized as an index to such toxic action on the liver. No changes in either the fructose tolerance or the fasting blood sugar level were observed in the cases reported in this article.

Cirrhosis is recognized as a complication of polycythemia vera.[25] I have seen one case in which there was slight retention of dye before treatment, suggesting the initial presence of some cirrhotic changes; in no case did the retention of dye increase in consequence of treatment.

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24. Baker, B. L., and Dodds, E. G.: Obstruction of Renal Tubules During Excretion of Hemoglobin, Brit. J. Exper. Path. **6**:247, 1925.

25. Levi, Ernst: Ueber die Ursache der Leber Cirrhose beim Polycythämie, Ztschr. f. klin. Med. **100**:777, 1924.

On the basis of the metabolic changes observed, one may conclude that the action of therapeutic doses of phenylhydrazine is limited largely to the destruction of erythrocytes with a resultant increase in the products of hemoglobin catabolism. Renal irritation may follow too large doses, but serious renal or hepatic injury was not observed.

SUMMARY

Patients with polycythemia vera, on a fixed diet, showed a negative nitrogen balance during the period of erythrocytic disintegration brought about by the administration of phenylhydrazine. An increased elimination of nitrogen of the urine in the form of urea occurred. The other nitrogen fractions of the urine were only slightly changed.

The total blood volume, hemoglobin and hematocrit were reduced. The total blood nitrogen was decreased. The nonprotein nitrogen of the blood was increased. The urea fraction accounted for most of this increase and is attributable to the production of urea in excess of the eliminative ability of the kidneys. Primary renal injury as a result of the administration of phenylhydrazine cannot be excluded. The amino-acid nitrogen of the blood was decreased. The creatinine and uric acid were only slightly changed.

The serum bilirubin was increased, with the occurrence of slight icterus. The van den Bergh reaction remained indirect throughout. An increase in urinary pigment coincided with the bilirubinemia. A change in carbohydrate metabolism was not demonstrated. Serious renal or hepatic injury was not observed. Characteristic changes in the heat exchange, as indicated by the basal metabolic rate, were not observed.

STUDIES IN ACROMEGALY

IV. THE BASAL METABOLISM *

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AND
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BOSTON

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Summary and Conclusions

In a preceding paper in this series by one of us (Davidoff) which deals with the anamnesis and symptomatology of acromegaly as recorded in 100 personally observed cases, a brief statement was made concerning the influence of the malady on the basal metabolic rate (B. M. R.[1]). It is proposed herein to discuss this matter more fully, for it is generally assumed that the thyroid is the organ exclusively concerned in the regulation of tissue combustion.

One may dismiss from consideration the many and often painstaking studies of the chemical pathology of acromegaly from the time of Schiff's article in 1897 [2] to that by Medigreceanu and Kristeller [3] in 1911. These early investigations tended to show that there is a retention of calcium and phosphorus in the disease, but the recorded observations were in large part contradictory. The studies were often complicated by the injection of inactive extracts or by the feeding of pituitary substance

* From the Surgical Service of the Peter Bent Brigham Hospital. The preceding papers in this series have been: I. Bailey and Davidoff: Concerning the microscopic structure of the hypophysis cerebri in acromegaly, Am. J. Path. **1**, 185-207, 1925. II. Davidoff: Historical Note. III. Davidoff: The Anamnesis and Symptomatology of One Hundred Cases, Endocrinology **10**:453, 1926.

1. For purposes of abbreviation these initials will be largely used to signify the basal metabolic rate in the succeeding pages.

2. Schiff, A.: Hypophysis und Thyreoidea in ihrer Einwirkung auf den menschlichen Stoffwechsel, Wien. klin. Wchnschr. **10**:277, 1897.

3. Medigreceanu, F., and Kristeller, L.: General Metabolism with Special Reference to Mineral Metabolism in a Patient with Acromegaly Complicated with Glycosuria, J. Biol. Chem. **9**:109, 1911.

in days when it was not appreciated that the anterior lobe principle is largely if not wholly destroyed in the stomach. Moreover, the tendency of the disease to undergo periods of varying activity or possibly to reach a permanently inactive stage was not then taken into consideration.

It was not until the principle of indirect calorimetry in the estimation of metabolism came to be introduced, largely as an outcome of the studies by Magnus-Levy, that the subject came to rest on its modern basis. In one of his earlier articles (1897) dealing primarily with the thyroid, the following statement was made:[4]

> In conclusion one more observation may be made concerning acromegaly. Virchow has already called attention to the similarity in the histologic character of the hypophysis and the thyroid gland, and today there is a great tendency to attribute to the hypophysis a rôle in acromegaly similar to that which the thyroid plays in Basedow's disease, and to treat that disease as the various disorders of the thyroid are treated, with organic extract (hypophysis, etc.). Certain, though of course not constant, symptoms of acromegaly resemble very much those of Basedow's disease: cardiac hypertrophy, exophthalmos, tachycardia, profuse sweats, copious urinary secretion, the appearance of polyphagia, glycosuria, and true diabetes. A combination of both diseases appeared to be present in a case recently studied at postmortem. In another case of acromegaly which was under my observation for a long while (hypophysis tablets without result), I also found continually an elevation of the gaseous exchange similar to the elevation found in Basedow's disease. A 52-year-old woman, of small stature, in an average of 12 experiments, used 270 ccm. O_2, 220.8 ccm. CO_2; i. e., with 52 Kg. 5.19 ccm. O_2, 4.25 ccm. CO_2 per kilo.
>
> These results, which, to be sure, do not agree with those given by Schiff in a case of acromegaly with symptoms of myxedema [*sic*] and a "retarded" metabolism, in any event invite renewed study of the metabolism and gaseous exchange in acromegaly.

Ten years later (1907), the statement was briefly repeated by Magnus-Levy in his section in van Noorden's "Handbuch," and since then the assumption that the thyroid is wholly responsible for the high metabolic rate occasionally seen in acromegaly has gained almost universal credence. But in these intervening years we have learned much that is new about this protean disease, and the question may therefore deserve reconsideration even though it may not be possible to answer it with finality.

Previous to 1909, the distinction between *hyper*pituitarism and *hypo*pituitarism was not well understood, or at least not fully emphasized. Many cases had come to be reported in the literature as ones of "pituitary tumor without acromegaly," and their possible relationship to what was known as adiposogenital dystrophy had been suggested, but it was not suspected, apparently, that these peculiar syndromes represented states the reverse of acromegaly. This was first made evident by

4. Magnus-Levy, A.: Untersuchungen zur Schilddrüsenfrage, Ztschr. f. klin. Med. **33**:269, 1897; Der Stoffwechsel bei Erkrankungen einiger Drüsen ohne Ausführungsgang, in Van Noorden: Handbuch der Pathologie des Stoffwechsels, ed. 2, 1907, vol. 2, p. 350.

the disclosure that an experimental hypophysectomy was likely to cause similar symptoms, namely adiposity, lethargy, subnormal temperature, sexual dystrophy and so on—symptoms which must therefore be caused from glandular deficiency. The experiments by Crowe, Cushing and Homans [5] which first made this clear were soon followed by Aschner's report [6] in which the influence of an hypophysectomy on the retardation of growth when it is performed on a young animal was first strikingly shown.

Although it was evident from their symptoms that these experimentally hypophysectomized animals must have a lowered tissue combustion, proof of this was first obtained in 1912 by Benedict and Homans.[7] Their painstaking studies which were carried out in the Carnegie Nutrition Laboratory showed a marked lowering of the metabolism of animals in a state of experimental hypopituitarism.

In the following year, 1913, on the opening of the Brigham Hospital, a laboratory under the direction of W. M. Boothby was equipped for the special purpose of investigating the metabolism of the ductless gland disorders. It was soon observed, in correspondence with the observations of Benedict and Homans, that patients with evident hypopituitarism showed on the whole a subnormal metabolic rate, whereas in the patients with acromegaly, as Magnus-Levy had long before pointed out, it was often considerably increased. The determinations for metabolism on the pituitary cases, however, in both this clinic and elsewhere, came to be subordinated to the intensive study of the metabolic rate in hyperthyroidism; for the latter proved to be more immediately of practical value not only as an indication of the activity of the thyroid disease, but also as a check on the effects of therapeutic measures, surgical or otherwise, employed to control it. Boothby's subsequent continuance of these studies at the Mayo Clinic led him to say in 1921:[8]

> The possible increased metabolic rate in active acromegaly, and the decreased rate in the syndrome known as hypopituitarism, suggest that alterations in the activity of the pituitary gland may change the metabolic level. There is, however, as yet little evidence that the secretion of any part of the pituitary gland is concerned with the normal rate of cellular combustion in the sense that it acts as a calorogenic agency.

These two sentences, if we understand them correctly, seem to be somewhat contradictory unless they carry the implication that the hypo-

5. Crowe, S. J.; Cushing, H., and Homans, J.: Experimental Hypophysectomy, Bull. Johns Hopkins Hosp. **21**:127, 1910.

6. Aschner, B.: Ueber die Funktion der Hypophyse, Arch. f. d. ges. Physiol. **146**:1, 1912.

7. Benedict, F. G., and Homans, J.: The Metabolism of the Hypophysectomized Dog, J. M. Research, **25**:409, 1912.

8. Boothby, W. M.: The Basal Metabolic Rate in Hyperthyroidism, J. A. M. A. **77**:252 (July 23) 1921.

physis can act only indirectly as a calorogenic agent through the mediation of the thyroid. But even this, if it can be proved, would be important to know.

THE METABOLIC RATE IN ACROMEGALY AND HYPOPITUITARISM

The observations on metabolism which form the basis of our present article were made on seventy-two of the one hundred cases of acromegaly in the Brigham Hospital records up to Aug. 1, 1926. Of these seventy-two patients, forty-nine showed the rate to be above normal, varying from + 2 per cent to + 61 per cent (average + 18.6 per cent). Eliminating all the cases with a rate below + 10 per cent as within the limits of normal, there remain thirty-two cases in which the average was + 26 per cent. In twenty-three patients the rate was below normal, ranging from — 1 per cent to — 17 per cent (average — 8.3 per cent). Only six of these twenty-three cases, however, showed a rate lower than — 10 per cent: one — 12 per cent, one — 13 per cent, two — 14 per cent, one — 16 per cent and one — 17 per cent.[9]

Although we are primarily concerned with the metabolism of acromegaly, it will be not amiss to contrast the figures given in the foregoing with the determinations for cases of pituitary insufficiency. In so doing, we will include only studies made on patients with hypopituitarism due to hypophysial adenomas which were histologically verified either at operation or at autopsy. We may thus avoid the complexities which are so often allowed to enter into the discussion of these subjects from the inclusion of a great variety of cases which are merely suspected of being pituitary cases.

Of the several hundred examples of clinical hypopituitarism which occur in the Brigham Hospital records, there are 107 with histologically verified chromophobe adenomas in which dependable metabolism determinations were also made. The average rate was — 14 per cent. Only four of the patients had a registration above zero: namely + 3 per cent, + 5 per cent, + 10 per cent and + 11 per cent. Seventy-one, or 66.3 per cent, had a rate below —10 per cent with an average of — 19.3 per cent; forty-six fell between — 10 per cent to — 20 per cent; twenty-one fell between — 20 per cent and — 30 per cent; four fell below — 30 per cent, the lowest being — 36 per cent.

9. These determinations have been based on the surface area as determined by the method of DuBois and on the standard formulated by him. In pituitary disorders, however, we are dealing oftentimes with bizarre persons—short, fat people with small extremities, and overgrown people with hypertrophied extremities. Hence the relation of the body surface to stature and weight may differ considerably from the average normal. It is possible, therefore, that the B. M. R. for pituitary cases, to be comparable, should be calculated from a modified formula.

These two sets of figures may be compared with those cited by Boothby and Sandiford [10] in a comprehensive analysis of their observations on metabolism made up to 1922 on conditions of all kinds at the Mayo Clinic. Their table includes determinations on thirty patients with acromegaly and on fifty-eight cases of so-called hypopituitarism. Of the thirty patients with acromegaly, 6.6 per cent showed a B.M.R. below — 10; 43 per cent fell in normal limits; and 50 per cent were above + 10, half of these being above + 20 per cent. On the other hand, of the fifty-eight cases of hypopituitarism, 53.5 per cent were below — 10; 34.5 per cent fell within normal limits, and only 12 per cent were above + 10 per cent.

For ease of comparison with our own determinations, these figures may be expressed as follows:

(*a*) Hyperpituitarism (Acromegaly) with Chromophile adenoma
Our figures show 45.8% of seventy-two cases above + 10%.
Boothby's figures show 50.0% of thirty cases above + 10%.

(*b*) Hypopituitarism with Chromophobe Adenoma
Our figures show 66.3% of 107 verified cases below — 10%.
Boothby's figures show 53.5% of 58 verified(?) cases below — 10%.

The figures from the two clinics are therefore essentially in agreement. The main difference appears to lie in the interpretation of the data. Whatever this may be, one may say with justifiable conviction: (1) that acromegaly, which is no less unmistakably a disorder due to hyperpituitarism than exophthalmic goiter is due to hyperthyroidism, often shows an elevated basal metabolic rate; (2) that the syndrome of pituitary insufficiency like myxedema shows a consistently lowered basal metabolic rate; (3) that the extreme variations in the rate, in accord with Magnus-Levy's statement already quoted, prove much greater in the disorders of the thyroid than in those of the hypophysis.

ACROMEGALY AND GOITER

The question now before us is whether a coincidental hyperthyroidism, either primary or secondary, is responsible for the increased rate often seen in acromegaly. As is well known, hyperthyroidism is not accompanied by any gross secondary changes in the hypophysis. Acromegaly, on the other hand, is commonly associated with a goiter of variable size which is often much larger than that which could be accounted for by the general splanchnomegaly of the disease. Hence it is natural to assume that the thyroid must be responsible for the accelerated tissue combustion; and there are certain facts which may be interpreted as lending support to this view, even though enforced recum-

10. Boothby, W. M., and Sandiford, I.: Summary of the Basal Metabolism data on 8,614 Subjects, with Special Reference to the Normal Standards for the Estimation of the Basal Metabolic Rate, J. Biol. Chem. **54**:783 (Dec.) 1922.

bency does not appear to influence the elevated metabolism in acromegaly so favorably as it does in hyperthyroidism.

In an earlier article in this series [11] it was pointed out that a palpable or definitely enlarged thyroid was recorded in twenty-five of the hundred patients with acromegaly. Of these twenty-five cases, seventeen happened to have reliable determinations of their metabolism, fifteen of them showing an elevated rate. To give the exact figures:

> In forty-nine cases with a B. M. R. of +3 per cent to +61 per cent, an enlargement of the thyroid was present in fifteen (30.6 per cent), three of the patients having had a thyroidectomy, with recurrence of the goiter in two of the three. On the other hand, in twenty-three cases with a B. M. R. of −2 to −17 per cent, only two (8.7 per cent) had palpably enlarged thyroids. Excluding the thirty-two cases with a rate between −10 per cent and +10 per cent as falling within the possible limits of normal, there remain seven cases with a rate below −10 per cent, and thirty-three with a rate above +10 per cent. Eight of the latter group had enlarged thyroids, whereas in none of those with definitely lowered metabolism was the gland appreciably enlarged.

The inference might therefore be drawn that an elevated metabolic rate in acromegaly and an enlargement of the thyroid go hand in hand, which is far from true, for in 75 per cent of the cases with definitely elevated metabolism the thyroid was not even palpable. We consequently must look for evidence from other sources, and it would seem at first sight that the problem involved should present no great difficulties of solution. As a matter of fact, it does, and a final answer may not be forthcoming until an active anterior-lobe principle is isolated, so that we can determine its independent effect on body metabolism and compare it with the reactions of thyroxin. However, while awaiting that time, light may be thrown on the subject by certain contributory observations. For if the thyroid is responsible, the excised gland should show the characteristic histologic changes of the exophthalmic or adenomatous goiter, and the metabolic rate should be definitely lowered by the procedure. If the acromegalic adenoma, on the other hand, is responsible, its excision or treatment by radiation should serve to lower the rate; and if it does so in the absence of goiter, the hypophysis may be considered to influence the metabolism independently of the thyroid.

THE QUESTION PRIMARILY FROM THE STANDPOINT OF THE THYROID

The thyroid as is well known is often enlarged in acromegaly, sometimes greatly so. When removed, as it may have to be because of dyspnea from tracheal compression,[12] if for no other reason, it has

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11. Davidoff, L. M.: Studies in Acromegaly. III: Anamnesis and Symptomatology of One Hundred Cases, Endocrinology **10**:461, 1926.

12. Cushing, H.: The Pituitary Body and Its Disorders, Philadelphia, J. B. Lippincott Co., 1912, p. 150, case 29.

usually proved to be a colloid goiter. Moreover, the gland as found and described at autopsy in cases of acromegaly has invariably been of the colloid type and free from those microscopic changes which are seen in hyperthyroidism. This would seem at first sight to speak strongly against the view that the increased metabolism so often met with in the disease is thyrogenic. But so far as we are aware, there is no recorded autopsy report in which recent ante mortem determinations for metabolism had been taken. It would be impossible to deny, therefore, that all these patients with colloid goiter were not by chance observed when the thyroid happened to be in an inactive or resting stage.

(*a*) *Thyroidectomy for the Goiter of Acromegaly.*—For more exact information one must therefore turn to surgery. However, though operations for hyperthyroidism are common, and though in most modern clinics the respiration apparatus is in general use, it is unusual for thyroidectomies to be performed on unquestioned cases of acromegaly; nor are these operations likely to be performed on patients in whom dependable preliminary estimations of the metabolic rate have shown that this rate is not definitely increased.[13] Fortunately for our purposes, we have had three such cases under observation. They are as follows:

CASE 1.—*Outspoken acromegaly in a middle-aged woman with large goiter and supposed hyperthyroidism in view of high B. M. R. Thyroidectomy: colloid goiter; lowering of B. M. R.*

Mrs. E. E. R., aged 47, referred by Dr. Horace Johnson of Brownville, Me., was admitted to the hospital on Feb. 26, 1917, with the following complaints: enlargement of the bones of the hands, feet and skull; goiter, dyspnea and nervousness.

Her childhood was without especial ill health. Catamenia appeared at 16. She was married at 28, and subsequently had four miscarriages, all during the third month of pregnancy. Regular menstruation continued till she was 45, when the menopause set in.

Her present illness dated from the age of 30, when she acquired a goiter which had not given her special trouble and had remained stationary in size for the past five years. Since she was young, there had been occasional attacks of cardiac palpitation with vomiting. Not long after the first appearance of the goiter, her hands and feet began to enlarge, and she had to increase the size of her gloves and shoes every few months. At the same time there was a great change in her features, accompanied by marked prognathism; there also was a definite increase in stature. Coincident with these changes in growth she gained nearly 40 pounds (18.1 Kg.) in weight (from 128 to 165 pounds) and experienced great fatigability, weakness and numbness of the extremities. Recently she had observed impairment of vision. At one time, a few months

13. The literature on the subject is meager. A few cases of hyperthyroidism in patients with acromegaly have been recorded but without B. M. R. determinations or operative verification (Claude, H.: Syndrome d'hyperfonctionnement des glandes sanguines chez des acromégaliques, Soc. de Biol. **59**:362, 1905.) Far more frequently a condition spoken of as myxedema has been described in cases of acromegaly with goiter. (Modena, G.: L'acromegalia, Riv. Sper. di Freniat. **29**:629, 1903).

before admission, there appeared to have been a period of subjectively observed hemianopia. She had no special complaint of headaches.

Sixteen months before admission she was deserted by her husband and had since been obliged to support herself. To this she ascribed her present dyspnea, for which she chiefly had entered the hospital. She had lost over 20 pounds (9.0 Kg.) in weight in the meantime.

Fig. 1 (case 1).—Patient with acromegaly, goiter, and elevated basal metabolic rate.

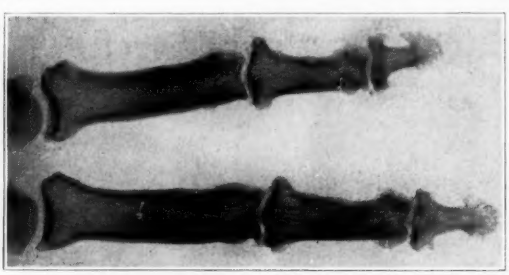

Fig. 2 (case 1).—Index and middle fingers to show telltale acromegalic phalangeal tufting with hyperostoses.

The physical examination showed a middle-aged woman (fig. 1) with typically acromegalic features, extremities and kyphosis. The roentgen ray showed the characteristic terminal phalangeal tufts (fig. 2) with hyperostoses of the bones elsewhere; also a greatly hypertrophied cranial vault about 2 cm.

in thickness, with mandibular prognathism. The sella was enlarged, measuring 30 mm. in an anteroposterior diameter and 25 mm. in depth (fig. 3). There were, however, no changes in the eyegrounds and no perimetric field defects. The heart was enlarged but compensation was good. The skin was bathed in sweat and considerably pigmented. Blood tests and urinalysis were negative.

The Goiter.—The gland was large and full but with no thrill or bruit. The pulse varied around 80, but occasionally rose to 120. The temperature tended to be slightly subnormal. The blood pressure showed some hypertension: systolic, 190; diastolic, 130. There were none of the eye signs of exophthalmic goiter; no tremor. Her B. M. R. on March 5 was + 61 per cent.

Here was a woman with unmistakable acromegaly and a large goiter compressing the trachea, as was shown by the roentgen ray. This appar-

Fig. 3 (case 1).—Greatly enlarged sella (natural size).

ently was the cause of her dyspnea. A recent accession of symptoms with nervousness and loss of weight even in the absence of marked tachycardia suggested a wave of hyperthyroidism which the unusually high metabolic rate served to substantiate. An operation was consequently decided on.

On May 5, 1917, Dr. Homans ligated the right superior thyroid artery. There was considerable reaction which subsided in a few days. On May 11, the B. M. R. was + 49 per cent.

On May 14 the left superior thyroid was ligated. Again there was considerable reaction which subsided. On May 19, the B. M. R. was + 52 per cent. On June 6, it had fallen to + 46 per cent; on June 25, it was + 48 per cent.

On June 27, Dr. Cheever performed a subtotal thyroidectomy under local anesthesia. The trachea was found considerably flattened. The gland (fig. 4) proved to be of the adenomatous colloid type, and although the epithelium was cuboidal, areas suggesting toxicity were not found. The patient made a rather poor convalescence with rapid pulse and fever for the first three days and a definite increase in her nervousness. On July 2, her B. M. R. was +62 per cent; on July 10, it had fallen to +31 per cent. She was discharged on July 13; her dyspnea was improved, but her symptoms were not greatly altered otherwise.

She was not heard from again until July 10, 1925, eight years later, when in reply to a letter of inquiry it was stated that, "Her general health seems very good, but she has occasional cardiac attacks with difficult breathing. She continues to have a very large appetite and is strong, but sleeps half the time. She will often be asleep ten minutes after her breakfast."

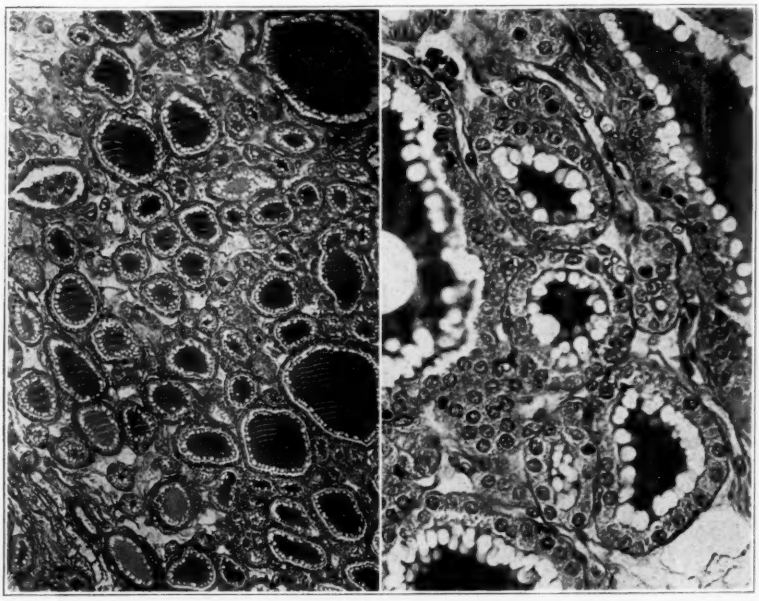

Fig. 4 (case 1).—Adenomatous thyroid. Hematoxylin and eosin stain; ×80 (left); ×300 (right).

Since a goiter of the type removed in this case is not usually associated with a marked increase in metabolism, one naturally must look for some other agency to explain the elevated metabolism. On the other hand, the elevated rate was reduced fully one half by the thyroidectomy. Whether one is to believe that the patient had a toxic goiter, histologic evidence of which is lacking in the opinion of several experienced observers, or that her high rate of metabolism was of pituitary origin and was lowered by the removal of a secondarily activated goiter, is a matter that might be argued. The history of the second case follows:

CASE 2.—*Incipient acromegaly with increased metabolism, operated on for coincidental goiter. Subsequent drop in the B. M. R. Advancing acromegaly with increase in the rate and a spontaneous drop to normal.*

Mrs. E. F., Swedish, aged 34, referred by Dr. Howard M. Clute of the Lahey Clinic, was admitted to the hospital on Oct. 8, 1925, with the complaint of acromegaly and its complications. She had had a small goiter since childhood. Her mother and sister also had goiter.

Enlargement of the extremities and features, with excessive sweating and hypertrichosis, had been apparent for possibly nine years. Headaches had lately become pronounced. Irregular menstruation for two or three years had been followed during the nine months previous to admission to the Brigham Hospital by total amenorrhea.

On Jan. 11, 1923, she had gone to the Lahey Clinic complaining of her goiter which recently had been rapidly increasing in size, and which had given

Fig. 5 (case 2).—Acromegalic woman after recent thyroidectomy for presumed hyperthyroidism.

her a sense of dyspnea on raising her arms. Associated with this she complained of nervousness, irritability, sweating and some pains in the arms and hands.

These symptoms were naturally ascribed to mild hyperthyroidism, and the view was supported when on January 24 the metabolic rate was + 24 per cent. There were no eye signs, no diarrhea nor tremor. The pulse had varied from 80 to 94. The menses were recorded as regular. The weight was 135 pounds (61.2 Kg.).

On January 25, a subtotal thyroidectomy was performed by Dr. Lahey for "a multiple colloid adenomatous goiter with secondary hyperthroidism." The patient made an excellent operative recovery. On Feb. 2, 1923, the B. M. R. was + 13 per cent; weight was 122 pounds (53.3 Kg.). On June 20, the metabolism had fallen to + 2 per cent, and on August 25 to — 3 per cent, with

an increase of weight to 131 pounds (59.4 Kg.). Her general condition remained unaltered. The goiter began to grow again, and she had been given Lugol's solution without effect. Her complaint of headache increased; it was suspected that she might have acromegaly, and in October, 1925, she was referred to the Brigham Hospital.

By this time the diagnosis was unmistakable (fig. 5); the sella was slightly enlarged (fig. 6), and the terminal phalangeal tufting was pronounced (fig. 7). On October 9, 1925, the B. M. R. was + 28 per cent; the weight was 134.2 pounds (60.8 Kg.). Visual field defects were not demonstrable, and she was discharged without treatment.

On November 23, her B. M. R. was + 3 per cent; and again on December 12, it was + 6 per cent. After this she was given a series of deep therapeutic

Fig. 6 (case 2).—Slightly enlarged sella.

radiations to the hypophysis. This was followed by subjective improvement in her headaches and in the numbness and tingling in her extremities.

On June 24, 1926, she was readmitted for study. Her general subjective improvement had continued. There appeared to be no increase in her acromegalism. Her B. M. R. was + 2 per cent; her weight was 134.8 pounds (61.0 Kg.).

Here, then, was another case of acromegaly with increased metabolism and an associated goiter which at operation proved to be of the colloid type. Doubtless the early acromegalic symptoms were obscured by the symptoms suggesting mild hyperthyroidism. Her metabolism of + 27 per cent dropped to approximately normal in the course of five

months after a subtotal thyroidectomy. Two years later, with increasing acromegalism and regrowth of her goiter, she had a metabolism of + 28 per cent, somewhat higher than before the thyroidectomy. This increased rate spontaneously subsided and has remained low. The accuracy of the observations can hardly be questioned. The interpretation is difficult. The third of these three cases follows:

CASE 3.—*Rapidly advancing acromegaly in a young woman with slightly increased B. M. R. A subtotal thyroidectomy for a supposed toxic goiter which proved to be of the colloid type. B. M. R. reduced.*

Miss B. M., aged 26, a stenographer, referred by Dr. W. A. Sullivan of Nashville, Tenn., was admitted to the hospital on Aug. 17, 1925, because of her rapidly advancing hyperpituitarism associated with a choked disk. Her outstanding complaint was of intolerable headache and discomfort in her throat.

Anamnesis.—Since childhood she had suffered from periodic "sick headache." About six years ago, when she was about 19 years of age, she began to have cephalalgia of another kind—pains in the head extending into the back and shoulders and associated with a gripping pain in the throat.

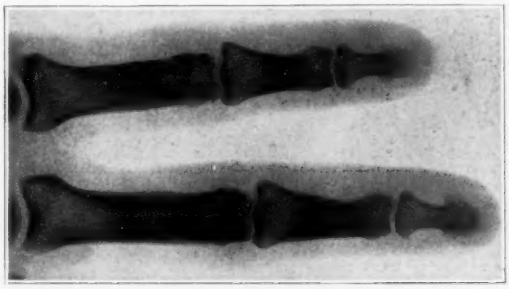

Fig. 7 (case 2).—Moderate terminal phalangeal tufting, a telltale of acromegaly.

It was not until 1921, two years later, that a marked enlargement of her extremities became noticable. Coincidentally, the change in her features was so great that she became unrecognizable to persons who had previously known her. From the beginning of the condition she had had a ravenous appetite, and there had been a progressive gain in weight: 116 pounds (52.6 Kg.) in 1919; 132 pounds (59.9 Kg.) in 1921; 140 pounds (63.5 Kg.) on admission.

Her menses began at the age of 12, continued to be regular until about eighteen months ago, and since August, 1924, amenorrhea had been complete. She had suffered all this time from marked hyperhidrosis and during the later stages of the disease from furunculosis.

She had undergone a variety of minor operations in the course of her malady. Most of her teeth, which had become widely spaced, had been extracted. Her tonsils and adenoids had been removed.

On April 9, 1924, a subtotal thyroidectomy had been performed by Dr. A. H. Kegel of Chicago, to whom we are indebted for the surgical history. She was supposed to have a toxic goiter in view of the symmetrically enlarged and pulsating gland associated with an elevated B. M. R. showing on three separate sessions + 35, + 35 and + 42 per cent.

The thyroid on removal proved to be merely a colloid goiter. No subjective improvement in the patient's condition followed the operation. Seven months

later she had been referred to the Mayo Clinic, where, in November, 1924, the B. M. R. was + 15 per cent. Her hypophysis had meanwhile been subjected to therapeutic radiations.

The physical examination on admission to the Brigham Hospital showed a young woman with hypertrophied extremities and features, puffy tissues, hypertrichosis of masculine type, hyperhidrosis, prognathism and the hyper-

Fig. 8 (case 3).—A young woman with *acromégalie fruste* after a thyroidectomy for supposed primary hyperthyroidism.

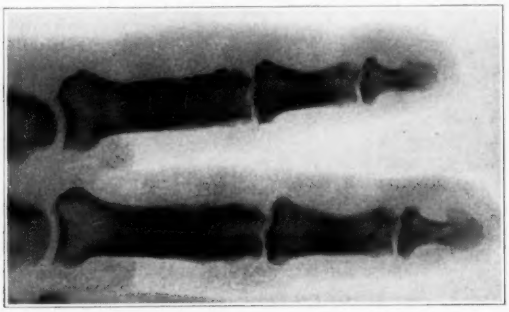

Fig. 9 (case 3).—Moderate tufting of terminal phalanges.

trophied tongue characteristic of outspoken acromegaly (fig. 8). The roentgen rays revealed the bony changes typical of the disease (fig. 9), but with a sella only moderately enlarged (fig. 10).

There was a left temporal hemianopia to colors, but instead of the usual pallor the disks showed a slight papilledema. She had also a relative anosmia, only strong odors being perceived. The heart was slightly enlarged. There was evidence of some hypertension: systolic pressure, 170; diastolic, 130. The urine was normal, without sugar or albumin. Her B. M. R. was + 5 per cent.

In view of the comparatively small sella and the distressing headaches accompanied by low grade of papilledema, an intracranial extension of her adenoma was suspected. She was given a roentgen-ray treatment and discharged. She did badly and reentered the hospital on Feb. 27, 1926. The evidences of overgrowth had definitely advanced. The clinical symptoms at the time were dominated by the signs of intracranial pressure. She had a high grade of choked disk which had progressed to blindness in the left eye and near blindness in the right. Her B. M. R. was + 10 per cent. A subtemporal decompression was performed disclosing a tense brain. The operation gave practically no relief.

The last report, received Sept. 24, 1926, was that her condition was becoming worse.

Fig. 10 (case 3).—Moderately enlarged sella of acromegaly.

Here again was a woman with a rapidly advancing acromegaly in whom a toxic adenoma was suspected because of her goiter and elevated metabolism. The goiter again proved to be of the colloid adenomatous type. Although her subjective symptoms were not improved, her B. M. R. after a period of seven months had fallen approximately to high normal levels; and a year later, possibly under the influence of hypophysial radiotherapy, the rate had dropped another 10 points. Meanwhile the hypophysial adenoma had evidently extended widely into the intracranial chamber.

Considering these three cases together, even though in all of them the B. M. R. was appreciably lower after the operations, one may conclude that in the absence of sufficient microscopic evidences of thyroid overactivity to account for the elevated metabolism which the patients

showed at the time of operation, this must be ascribed to some cause other than to hyperthyroidism alone.[14]

(*b*) *The Effect of Lugol's Solution.*—Mention was made, in the notes on the second case, of Lugol's solution having been employed without the expected effect; this, with one notable exception, has been our experience in the few cases under our personal observation in which it has been administered to patients with acromegaly with increased metabolism and enlarged thyroid glands. In one patient, for example, with a metabolic rate of + 26 per cent, 5 drops of Lugol's solution three times a day was administered over a period of fourteen days, and the B. M. R. rate estimated every forty-eight hours, without the slightest effect being shown; whereas ten days after a hypophysectomy it had dropped to zero and remained there. The exception was a recent observation, which proves to be a most striking one:

Case 4.—The patient, Miss E. A. C., a school teacher, aged 35, first came under observation on Nov. 15, 1913. She was a cooperative and intelligent woman with marked acromegalic changes of four years' duration. Eight months later (July 16, 1914), owing to increasing headaches, asthenia and beginning bitemporal constriction of her fields of vision, she was readmitted to the hospital and a transphenoidal operation was performed. A tense gland was encountered, and a fairly radical intracapsular removal of adenomatous tissue (chromophile) was carried out.

She made an excellent recovery, with marked subjective improvement in headaches, vision and size of the extremities. This improvement lasted for nearly eight years, although there was in the interval an obvious increase in her acromegalic appearance.

In the summer of 1921 she began to notice a definite thyroid enlargement associated with "nervousness," the symptoms improving under iodine. During the next four or five years the thyroid progressively enlarged, and although she continued to be nervous and to show periodic waves of glycosuria, she managed to continue her teaching.

She came under observation again in November, 1925, with a mild diabetes. Her basal metabolism was then taken for the first time, the rate averaging + 41 per cent and + 39 per cent on two different occasions. She, however, did not have marked tachycardia, the pulse rate being about 90; her temperature tended to be subnormal and there was some doubt of her actually having thyreotoxicosis

She recently returned for the purpose of submitting to a test with Lugol's fluid. The thyroid was even more enlarged, her metabolism was still high and she complained of nervousness and sleeplessness. There was, however, no tachycardia, the pulse averaging 80; her temperature was normal, and she was in a period of freedom from glycosuria. The complete list of her metabolism determination may be here assembled, and it should be pointed out that between July 8 and August 13 she had been resting and taking heliotherapy under most favorable circumstances.

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14. In a personal communication, Dr. Irene Sandiford of the Mayo Clinic writes, on Aug. 17, 1926, that thyroidectomy has been performed there on fourteen patients with acromegaly; thirteen times for toxic adenoma and once for exophthalmic goiter; that in only nine of the cases were rates taken both before and after the operation; that of these nine, five showed increased or only slightly decreased postoperative rates, and four showed normal rates.

Nov. 26, 1925..... + 41
Nov. 30, 1925..... + 39
July 8, 1926..... + 37
Aug. 13, 1926..... + 34

Lugol's solution begun, 5 drops, three times a day.

Aug. 16, 1926..... + 29
Aug. 18, 1926..... + 21
Aug. 20, 1926..... + 18
Aug. 23, 1926..... + 21
Aug. 25, 1926..... + 23
Aug. 27, 1926..... + 12
Aug. 31, 1926..... + 10

Lugol's solution discontinued.

Sept. 2, 1926..... + 6
Sept. 4, 1926..... — 1

This extraordinary and progressive drop in the metabolism under the administration of Lugol's solution was almost more than one would expect in exophthalmic goiter; and in the experience of this hospital the metabolism of the patient with ordinary toxic adenomatous goiter is unaffected by Lugol's solution. The patient meanwhile experienced marked subjective improvement. She slept more soundly than usual, was free from nervousness, and the large goiter became perceptibly smaller, hard and nodular. Certainly the response was as definite as one ever sees in thyrotoxicosis. The patient, unfortunately, had to leave for her school before we could learn whether there was to be a reelevation of the rate, which continued to drop for four days after the Lugol's solution was discontinued.

We may therefore conclude that Lugol's solution is capable in certain cases of lowering the increased metabolic rate of acromegaly in a striking way, and might naturally assume that it does so by an effect on the thyroid.

To this point the testimony would seem to be largely in favor of the thyroid, it being assumed that the colloid goiters, which have been observed, merely represent the end stages or temporary resting periods of waves of hyperthyroidism, this, according to Marine's view, being the way in which a colloid goiter is formed. The tissues in the first case, though pronounced a colloid thyroid (fig. 4), have a definitely active look even though the picture does not bear resemblance to that of a toxic goiter. How quickly the picture of exophthalmic goiter may change under the effects of iodine to that of a colloid goiter has recently been well shown by Rienhoff.[15]

It must not be forgotten that a number of cases of exophthalmic goiter have been described as coexistent with acromegaly. The perusal of the case histories, however, leaves one somewhat in doubt as to the dependableness of the diagnoses, the cases being no more convincing

15. Rienhoff, W. F.: Involutional or Regressive Changes in the Thyroid Gland in Cases of Exophthalmic Goiter and Their Relation to the Origin of Certain of the So-Called Adenomas, Arch. Surg. **13**:391 (Sept.) 1926.

than the three herein reported; and the puffiness of the eyelids with protrusion of the eyeballs from increase in intra-orbital tissues often seen in acromegaly, might easily mislead the unwary. But, all told, there is nothing in the evidence so far that would contradict the possibility that primary hyperthyroidism and primary hyperpitutarism may coexist in the same patient.

THE QUESTION FROM THE STANDPOINT PRIMARILY OF THE HYPOPHYSIS

On the principle that removal of the goiter, or its direct treatment by radiation in cases of hyperthyroidism causes a symptomatic improvement, of which the lowering of the basal metabolic rate proves to be a more or less satisfactory measure, one might assume that corresponding procedures on the hypophysis in cases of hyperpituitarism with increased metabolism ought to show comparable effects. Although for a number of reasons the observations on which the test of this assumption must rest are few, they appear to be fairly conclusive.

(*a*) *The Effect of Radiation.*—It has been unusual for patients in the series to be subjected to hypophysial radiation alone, nor have those so treated often appeared to be greatly benefited thereby. Unusually there have been definite indications necessitating operative intervention, and several of these patients have been treated by a combination of surgical measures and subsequent radiation. An occasional patient, however, has been given roentgen-ray treatment alone and has shown a subsequent fall in metabolism with definite improvement in symptoms. The following is an example:

CASE 5.—*Outspoken acromegaly in an adult male, treated by deep hypophysial radiation. Subsequent fall in B. M. R.*

C. H. W., a huge acromegalic man, aged 46, first entered the hospital on July 13, 1925, complaining of his disfigured appearance, somnolence, irritability, poor memory, pain and tingling in the feet, fainting spells and excessive perspiration. His sella turcica was moderately enlarged, but his visual acuity, optic disks and fields of vision showed no variations from normal. The B. M. R. was + 40 per cent. The thyroid was not palpable.

In the absence of any pressure symptoms, he was given a series of deep roentgen-ray radiations. Treatments were begun here on July 17, 1925, and continued with approximately three week intervals, under adequate supervision, in another city until six treatments had been given. On September 8, his metabolic rate had dropped to + 29 per cent, and October 1 to — 10 per cent. Meanwhile he experienced definite improvement in his symptoms.

In the course of two months after his last radiation his condition had definitely retrogressed, and he was readmitted to the Brigham Hospital, where on January 15, 1926, his B. M. R. was again found to be + 45 per cent. Another series of roentgen-ray treatments was begun, and these were again followed by definite subjective improvement. By June 30, 1926, the rate had dropped to + 24 per cent, and on October 13, when he reported here to have his condition checked up, it was found to be + 10 per cent. He has not been so free from his distressing symptoms of "acromegalism" for years.

(*b*) *The Effect of Operation.*—Far more significant and striking are the results of the surgical procedures. Formerly, operations for pituitary tumors were carried out with the single object of relieving the optic chiasm from pressure and saving vision. In this sense they were comparable to the early operations for goiter which were conducted solely for the relief of dyspnea due to compression of the trachea. In each instance the disturbances were mechanical, and mechanical procedures were needed to relieve them.

Operations on the thyroid, however, have long since passed beyond this early and restricted use, and are now largely employed to counteract the toxic effects of hyperthyroidism, which does not necessarily imply a large tumor. Just so we may expect hypophysial operations, although technically far more difficult, to be employed more and more often in acromegaly to counteract the effects of the hyperpituitarism irrespective of the size and pressure effects of the adenoma.

In either case, the size of the tumor is no measure of the activity or severity of the disease. What concerns us far more than size is the relative amount of tissue removed, for a mere decompression of the sella to relieve pressure symptoms in a case of acromegaly should have no effect in changing the metabolic rate. With the improvement in the technic of these operations in recent years, the extirpation has become increasingly radical, and the effects in modifying the symptoms are becoming more lasting, more definite and more nearly comparable to the effects of a subtotal thyroidectomy.

Even though the number of hypophysectomies for uncomplicated acromegaly on which reliance may be placed is few, they are sufficiently definite for our present purposes. As it happens, dependable metabolism determinations were made in only thirty-nine of the fifty-six acromegalic patients in the series subjected to operation and in only eighteen of these thirty-nine cases are both preoperative and postoperative observations recorded. Before operation the eighteen cases showed a B. M. R. ranging from — 14 per cent to + 32 per cent (average, + 10 per cent); after operation they ranged from — 19 per cent to + 13 per cent (average — 7 per cent), showing a total average drop per case of 17 per cent.

This disclosure that not only the patients with originally high determinations but also those with a low or even subnormal preoperative B. M. R. showed on the average a significant lowering of the rate subsequent to operation, suggests that the operation per se might be responsible, particularly since in several of these cases the amount of adenomatous tissue removed was not particularly great. The postoperative determinations were deferred until the patient had fully recovered from the immediate effects of the operation and was up and about the ward. But there are sufficient reasons to discard this possible

explanation of the postoperative fall in rate, for such comparable changes in the rate are not seen in the patients operated on for pituitary adenomas with hypopituitarism. These operations are more common and the extirpation more likely to be radical, and yet the metabolism determinations are likely to remain, on the average, approximately at their former level.

In a series of twenty-four patients with hypopituitarism associated with surgically verified chromophobe adenomas, in whom metabolism studies were made both before and after operation, the results were as follows: Before operation the twenty-four patients showed a metabolic rate ranging from — 32 per cent to — 3 per cent (average — 16.1 per cent); after operation they ranged from — 39 per cent to — 5 per cent (average — 17.7 per cent), showing a total average drop of only 1.6 per cent. The contrast between these patients and those with acromegaly may be seen at a glance in table 1.

TABLE 1.—*The Basal Metabolic Rate of Patients with Acromegaly and That of Patients with Hypopituitarism*

	Number of Cases	Average Basal Metabolic Rate		Average Drop in Metabolic Rate
		Before Operation	After Operation	
Acromegaly	17	+10.0%	— 7.0%	17.0%
Hypopituitarism	24	—16.1%	—17.7%	1.6%

In addition to the fall in metabolism, the acromegalic patients are likely to have a distinct and early change in appearance so far as the malady affects the soft parts. This is shown by a definite improvement in the texture of the skin, a distinct reduction in the size of the hands and feet, often first noticed by the patient himself. That the change is not born of the patient's expectancy is shown by actual change in measurements, to be accounted for by the disappearance or lessening of the peculiar acromegalic "myxedema." Associated with this improvement in the extremities there is often a considerable loss of weight, not infrequently 10 or 12 pounds (4.5 or 5.4 Kg.); this can hardly be ascribed to the operation itself, which is remarkably well borne by these patients, and a corresponding loss of weight does not occur after similar operations on patients with hypopituitarism.

It would appear, therefore, that the further lowering of even a subnormal metabolism in the series of patients with acromegaly may have some significance, and that our formula for calculating the rate in these patients may place the normal too high.[16] However this may be, the cases in which a definitely elevated rate of + 10 per cent or more was

16. The Harris-Benedict standard in general gives values 5 per cent lower than the DuBois standard, and Dr. Benedict has recently suggested that the standard for women should be 5 per cent lower than this.

lowered by the operation are sufficiently striking to bear alone the brunt of the argument. There are nine cases that fall in this group, the changes in rate which had taken place in about two to three weeks after operation being shown in table 2.

These were all outspoken examples of acromegaly. Only one of the patients had a palpably enlarged thyroid. Another had a condition of complicating diabetes which, however, should not have modified the metabolic rate. The majority of them had large pituitary adenomas giving local pressure symptoms, although in one of them the gland was only slightly enlarged and in another scarcely enlarged at all (case 7). Brief abstracts of the histories are given below:

CASE 1.—Mrs. H., a Hungarian woman, aged 24, was admitted to the hospital on March 15, 1916. She had been married at 19 and a year later had given birth to a normal child. Following this pregnancy, her menses were never restored. She soon began to have severe headaches and photophobia with marked weakness and drowsiness, numbness of the extremities and excessive sweating, accompanied by enlargement of the extremities and features.

TABLE 2.—*Changes in the Basal Metabolic Rate Before and After Operation*

Case	Complications	Before Operation	After Operation
1	Goiter	+18	+ 2
2	.....	+15	+ 3
3	.....	+21	+ 6
4	.....	+31	+13
5	.....	+32	+12
6	Diabetes	+28	+13
7	Glycosuria	+25	0
8	.....	+24	+ 4
9	.....	+16	+ 3

Examination showed a typical acromegalic patient with an enlarged thyroid, but tremor, tachycardia, exophthalmos or other evidences of hyperthyroidism were not present. The sella was much enlarged (21 mm. by 17 mm.), and although there was some pallor of the disks, the visual fields were normal.

On March 17, her height was 158 cm. (5 ft. 3 in.), her weight 158.4 pounds (71.8 Kg.); the pulse rate was 88, the temperature 98.6, and the B. M. R. + 18 per cent.

On March 24, a transphenoidal operation was performed in the hope of relieving her severe headaches even though evidence of chiasmal pressure was lacking. The dura was under great tension, and on opening it tense (chromophile) adenoma began to extrude and a considerable amount of it, for the time (1916) was removed. The patient made an excellent recovery, with complete relief from headaches.

On April 5, her weight was 147 pounds (66.7 Kg.), temperature, 98.7 F., pulse rate 69 and B. M. R. + 2 per cent.

Here, then, was a patient with an enlarged thyroid and slightly increased metabolism whose metabolic rate dropped 16 per cent subsequent to an uncomplicated operation on the hypophysis with partial removal of an adenoma. The following cases all represent similar procedures with corresponding results on patients without palpable enlargement of the thyroid.

Case 2.—Mrs. B. F., aged 23, was admitted to the hospital on Feb. 20, 1914. Symptoms of acromegaly were first noticed three years previously during her first and only pregnancy. A healthy child was born, which was breast fed. Normal catamenia never became reestablished. In addition to the acral overgrowth, there were polyphagia, headaches, darkening of the skin, increased hirsutes, deepening of the voice, and other symptoms.

Examination showed a moderately enlarged sella but no eye changes. Determinations for metabolism were not made.

In December, 1914, she again came under observation. Her symptoms were definitely increased, and there were beginning bitemporal field defects and a further enlargement of the sella.

On Oct. 21, 1915, she reentered the hospital for operation owing to a still further advance in symptoms. From the time of her first admission she had gained 35 pounds (15.9 Kg.).

On October 27, her height was 171.5 cm. (5 ft. 8½ in.), weight 190.8 pounds (86.4 Kg.), temperature, 98.4 F., pulse rate 88 and B. M. R. + 15 per cent.

On October 27, a transphenoidal operation was performed with sellar decompression and fragmentary removal of an adenoma, which was shown to be chromophilic. Convalescence was uneventful.

On November 9, her weight was 182 pounds (82.6 Kg.), temperature 98.8 F., pulse rate 80, and B. M. R. + 3 per cent.

Case 3.—Mrs. J. A. L., aged 33, was admitted to the hospital on Jan. 8, 1917, with a history of obvious acromegaly of about eight years' duration. Onset with headaches, enlargement of extremities, numbness and tingling, asthenia, drowsiness, nervousness, increase in weight from 142 to 170 pounds (64.4 to 77.1 Kg.), irregular menstruation, increase in hirsutes, and other symptoms.

Examination showed advanced acromegalic changes with a moderately enlarged sella and early bitemporal field defects. The thyroid was palpable. She had enormously enlarged tonsils which were giving her trouble, and these were removed. She reentered the hospital three months later.

On April 4, 1917, her height was 157 cm. (5 ft. 2½ in.), weight 149.8 pounds (67.8 Kg.), temperature 97.8 F., pulse rate 80, and B. M. R. + 21 per cent.

On April 9, a transphenoidal operation was performed with extirpation of a considerable amount of adenomatous tissue which proved to be acidophilic. Convalescence was uneventful; there was marked improvement in appearance.

On April 23, her weight was 143.8 pounds (65.1 Kg.), temperature 98.6 F., pulse rate 72, and B. M. R. + 6 per cent.

She was not seen again until two years later. She was greatly improved, although she still experienced occasional exacerbations of her previous symptoms. Curiously enough, normal menstruation had become reestablished. The B. M. R. was not taken.

Case 4.—Joseph S., a machinist, aged 20, admitted to the hospital on March 24, 1924, had rapidly advancing acromegaly of only seven months' duration. His symptoms were: rapid increase in the size of the extremities and face; a period of marked glycosuria, blurring of vision, drowsiness, apathy, increase in weight and impotence.

Examination showed in addition to the marked overgrowth a large sella, optic atrophy and bitemporal hemianopia.

On March 25, his height was 174.5 cm. (5 ft. 9¾ in.), weight 156.2 pounds (70.9 Kg.), temperature 98.5 F., pulse rate 83, and B. M. R. + 31 per cent.

On April 5, a transphenoidal operation was performed with fairly extensive removal of adenomatous (acidophilic) tissue. Convalescence was uneventful. A postoperative B. M. R. estimation was not made. The patient was given a series of roentgen-ray treatments and temporarily passed from observation with a marked change for the better in his appearance.

On Feb. 26, 1925, his weight was 147 pounds (66.7 Kg.), temperature 98.6 F., pulse rate 74, and B. M. R. + 13 per cent.

CASE 5.—Mrs. F. P., aged 48, was admitted to the hospital on April 19, 1925, with a history dating back fourteen years when, in association with headaches and photophobia, acromegalic changes became pronounced. Subsequently amenorrhea, lethargy, disturbance of vision, excessive sweating, increase of weight, loss of strength, polyphagia and other symptoms appeared. Examination showed a large sella, optic atrophy and blindness in the right eye with left temporal hemianopia. There was no glycosuria, and the thyroid was not palpable.

On April 22, her height was 165.6 cm. (5 ft., 6 in.), weight 179.7 pounds (81.4 Kg.), temperature 98.4 F., pulse rate 84, and B. M. R. + 32 per cent.

On April 28, a transphenoidal operation was performed with extensive removal of adenomatous tisue found to be eosinophilic. Convalescence was uncomplicated, and there was definite improvement in symptoms.

On May 14, her weight was 173.1 pounds (78.5 Kg.), temperature 98 F., pulse rate 98, and B. M. R. + 23 per cent.

On May 20, her weight was 175.1 pounds (79.4 Kg.), temperature 98 F., pulse rate 84, and B. M. R. + 12 per cent.

CASE 6.—R. H., a farmer, aged 41, was admitted to the hospital on Nov. 25, 1925, with a history of progressive acromegaly over a period of nineteen years. A condition of complicating diabetes had been observed for six years. Examination showed a full-blown example of the disease with large sella, optic atrophy, and one eye completely blind. The thyroid was not palpable.

On November 27, his height was 172.8 cm. (5 ft., 9.1 in.), weight 159.7 pounds (72.3 Kg.), temperature 97.2 F., pulse rate 81 and B. M. R. + 38 per cent. His B. M. R. was studied on various occasions before and after the administration of insulin and before and after the administration of Lugol's solution; neither had any appreciable effect.

On December 23, a transphenoidal operation was performed with extensive removal by suction of soft adenomatous tissue which proved to be acidophilic. There was an uncomplicated convalescence with subjective improvement.

On Jan. 1, 1926, his weight was 157 pounds (71.2 Kg.), temperature 98.2 F., pulse rate 96, and B. M. R. + 30 per cent.

January 27, his weight was 164.7 pounds (74.6 Kg.), temperature 97 F., pulse rate 80, and B. M. R. + 13 per cent.

CASE 7.—Mrs. Lucia S., an Italian woman, aged 22, was admitted to the hospital on Dec. 17, 1925. Two years before, during a pregnancy, there had been an onset of her present illness with severe headaches, marked increase in weight and enlargement of the extremities. The menses were normal. The thyroid was barely palpable; the sella was scarcely enlarged, and there were no eye signs; the pulse rate was from 80 to 90.

The patient was readmitted on Aug. 27, 1926, with a history of continued severe headaches.

On August 30, her height was 157 cm. (5 ft., 2 in.), weight 204 pounds (92.5 Kg.), temperature 98.4, pulse rate 84, and B. M. R. + 25 per cent. The B. M. R., which was repeated in two days, was + 24 per cent.

On September 2, the administering of Lugol's solution, 5 drops three times a day, was started and continued for fourten days—until September 16.

On September 4, the B. M. R. was + 19 per cent.
On September 7, the B. M. R. was + 26 per cent.
On September 9, the B. M. R. was + 25 per cent.
On September 11, the B. M. R. was + 20 per cent.
On September 14, the B. M. R. was + 16 per cent.
On September 16, the B. M. R. was + 21 per cent.

On September 20, a transphenoidal operation, with radical hypophysectomy, was performed. There was immediate relief of headache and prompt and uneventful recovery from operation, with marked improvement in acromegaly.

On September 30, the patient's temperature was 97 F., pulse rate 87, weight 196 pounds (89 Kg.), and B. M. R. $\mp$ 0 per cent.

Case 8.—Miss S. M., a Jewess, aged 23, was admitted to the hospital on April 22, 1926. Onset of the illness with severe headaches and enlargement of extremities had occurred at the age of 15. She did not have amenorrhea. Glycosuria was not present, but a low tolerance for sugar. The thyroid was not palpable. The pulse rate was 80. There was a slightly enlarged sella, pallor of optic disks and beginning upper bitemporal field defect.

On April 23, her height was 171 cm. (5 ft., 8.4 in.), weight 176.1 pounds (79.8 Kg.), temperature 98 F., pulse rate 93, and B. M. R. + 24 per cent.

On May 10, a transphenoidal operation was performed with radical removal of eosinophilic adenoma. Convalescence was uncomplicated with marked improvement in symptoms.

On May 28, her weight was 168 pounds (76.2 Kg.), temperature 99.2 F., and B. M. R. + 4 per cent. The patient was discharged from the hospital.

Case 9.—David M., a Jew, aged 36, was admitted to the hospital on June 22, 1926. The disease was of ten years' duration. He was admitted on account of increasing headaches and loss of vision. There was outspoken acromegaly with a large sella and bitemporal hemianopia. Glycosuria was not present, but low tolerance for sugar was demonstrated. The thyroid was not palpable. The pulse rate was variable, averaging 70.

On June 23, his height was 167 cm. (5 ft., 6.8 in.), weight 161 pounds (73.0 Kg.), temperature 98.6 F., pulse rate 73, and B. M. R. + 16 per cent.

On July 2, a transphenoidal operation with fairly radical excision of chromophilic adenoma was performed. There was an uncomplicated recovery with marked improvement in both local and general symptoms.

On July 12, his weight was 149.8 pounds (67.8 Kg.), temperature 98.2 F., pulse rate 66, and B. M. R. + 3 per cent. The patient was discharged from the hospital.

On September 24, he reentered the hospital for a metabolism test and the B.M.R. was found to remain low, + 2 per cent.

None of these nine patients showed any clinical evidence of hyperthyroidism. One of them had a palpably enlarged thyroid, but like the others did not show tachycardia, tremor or exophthalmos. It would seem, therefore, unless there is some point in the argument which has escaped us, that these cases meet the essential criteria, namely, that patients with acromegaly who have an elevated metabolic rate in the absence of clinical symptoms of hyperthyroidism show a distinct drop in the preoperative rate after partial removal of the hypophysial adenoma, which inevitably is of the acidophilic type known to accompany hyperpituitarism.

SUMMARY AND CONCLUSIONS

1. Acromegaly is a disease which bears the same relation to pituitary insufficiency (hypopituitarism) that exophthalmic goiter bears to myxedema (hypothyroidism). It is, in other words, an expression of hyperpituitarism just as exophthalmic goiter is of hyperthyroidism.

2. Acromegaly is often accompanied by an elevated basal metabolic rate and the reverse condition of hypotuitarism by a subnormal rate.

3. Acromegaly, furthermore, is often accompanied by a palpably enlarged thyroid and by symptoms suggesting thyreotoxicosis to which the increased basal metabolic rate has generally been ascribed.

4. Occasionally the goiter in cases of acromegaly has been operated on under the assumption that the symptoms were due to primary hyperthyroidism. The gland in three such cases has been found to show merely colloid changes of adenomatous type without the expected evidences of toxicity. Nevertheless, thyroidectomy has served to lower the metabolic rate, and Lugol's solution has also been shown capable of lowering it.

5. On the other hand, operations on the chromophilic hypophysial adenoma itself in cases of acromegaly in which the basal metabolism is elevated, even in the absence of a palpably enlarged thyroid, are followed by a fall in the metabolic rate almost as uniformly and strikingly as are the operations on the thyroid in exophthalmic goiter.

6. One may conclude that the chromophilic cells of the anterior lobe of the pituitary body secrete a substance which not only contains the hormone of growth, but which is capable of raising the basal metabolic rate. Whether the hypophysial principle under these circumstances acts as a stimulus to metabolism directly on the tissues or only through the intermediation of the thyroid cannot as yet be positively stated, although there are reasons to believe that it may act independently.

7. In either event, whether the effect is primary or secondary, the elevation of the metabolic rate may properly be ascribed to the hyperpituitarism.

ADDISON'S DISEASE AND DIABETES MELLITUS OCCURRING SIMULTANEOUSLY

REPORT OF A CASE *

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The combination of diabetes and Addison's disease appears from the literature to be of extremely rare occurrence. Heller [1] found this association only once in 800 cases of Addison's disease reviewed by him. Although there are five cases in the entire literature in which the authors state that the patients have had diabetes in conjunction with Addison's disease, the diagnosis in every one of these cases may be questioned. The only evidences of diabetes in the patient referred to by Heller were somnolency and a strongly positive reaction for acetone in the urine. Nothnagel,[2] who originally reported this case, referred to it merely as one of Addison's disease with severe cerebral manifestations. Of the four remaining cases, certainly that of Rabé [3] and possibly that of West [4] were instances of tuberculosis of the suprarenal glands with hemochromatosis and glycosuria. In the former case this diagnosis was proved by pathologic studies. In West's case, owing to the loss of the notes on the autopsy, accurate pathologic description is not available; however, the enlargement of the liver noted prior to death suggests the diagnosis of hemochromatosis in this case also. At any rate, the evidence presented does not warrant the diagnosis of Addison's disease, especially since mention is not made of the existence of hypotension, asthenia or gastro-intestinal symptoms. Finally, two cases [5] of diabetes and tuberculosis involving one or both suprarenal glands have been reported. In neither case were pigmentation, weakness, gastro-intestinal symptoms or hypotension noted. Neither could therefore be said to present the syndrome of Addison's disease.

REPORT OF CASE

History.—The patient, aged 39, who came under the observation of Dr. John H. Musser, Jr., at the Presbyterian Hospital, Philadelphia, for the first time on May 7, 1924, gave a history of having always been subject to headaches, but said that otherwise she had been in good health. She had married at the age of 26

* From the Medical Division of the University Hospital.
* Read before the Section on General Medicine of the College of Physicians.

1. Heller, J.: Deutsche med. Wchnschr. **33**:1216 (July 25) 1907.
2. Nothnagel, H.: Ztschr. f. klin. Med. **9**:195, 1885.
3. Rabé, M.: Bull. et mém. Soc. anat. de Paris **75**:459 (May) 1900.
4. West, S.: Tr. Path. Soc. London **41**:271, 1890.
5. Montgomery, C. M.: A Case of Diabetes Mellitus Associated with Tuberculosis of the Adrenal Glands, J. A. M. A. **58**:847 (March 23) 1912. Ogle, J. W.: St. George's Hosp. Rep. **1**:178, 1866.

and had had five pregnancies, one being a two months' miscarriage; one child had died of pneumonia in infancy. The remaining three children were healthy. There was no history of severe illness or abdominal trauma which might explain simultaneous pancreatic and suprarenal disease, nor was there any history of exposure to silver or any other metal to account for the generalized pigmentation. She spent the summer of 1923 at the seashore, and was, as she believed at the time, tanned by exposure to the sun. After returning to the city, the color of her skin remained dark, and as the winter progressed, instead of becoming lighter, it became darker. About December, 1923, she began to complain of weakness, loss of energy, nausea and exacerbation of the headaches. For these symptoms she consulted an ophthalmologist and a dentist, who did not find anything abnormal. She began to lose weight, and about April 23, 1924, polyuria, polyphagia and polydipsia made their appearance. On May 5, she was so weak that she was forced to remain in bed. She was nauseated and vomited all that night.

Examination.—Sugar was found in the urine. A diagnosis of diabetes was made, and the patient was sent to the Presbyterian Hospital under Dr. Musser's care. At this time she was drowsy, could be only partially aroused and could not answer questions. Her blood sugar content was 0.44 per cent, and she was obviously in a state bordering on coma.

Treatment and Course.—During the first twenty-four hours she was given 293 Gm. of carbohydrate in the form of glucose by rectum, orange juice and glucose by mouth and 100 units of insulin. The specimen of urine contained 7.2 Gm. of sugar for this day, but some may have been lost, for on the following day 22.5 Gm. were passed, 75 units of insulin being given. At this time the patient weighed 99½ pounds (45.1 Kg.), 20 pounds (9 Kg.) under her usual weight. In five days the urine became sugar-free and continued so for the remainder of the patient's stay in the hospital. She suffered three insulin shocks during the period of her stay, these occurred on days when she received, respectively, 80, 80 and 50 units of insulin and 60, 40 and 40 Gm. of carbohydrate. She was discharged from the hospital on June 11, 1924, feeling well, taking 20 units of insulin before breakfast, 10 units before lunch and 20 units before supper. Her diet at this time consisted of 55 Gm. of protein, 160 Gm. of fat, and 90 Gm. of carbohydrates. On this regimen she felt well, and in six months gained 21 pounds (9.5 Kg.) although sugar was present in her urine at times. From this time on glycosuria gradually became more and more difficult to control, and when, on Dr. Musser's leaving Philadelphia, she came under my observation, specimens of her urine contained sugar much of the time.

On Oct. 10, 1925, her urine contained diacetic acid and vomiting commenced. She entered the University Hospital. Her blood sugar on admission was 0.255 per cent and the carbon dioxide content of her blood plasma was 35 per cent by volume; under treatment, four days later, this figure rose to 54. The urine was pale yellow, clear, acid, had a specific gravity of 1.020, contained a normal number of leukocytes but no albumin, casts, cylindroids or erythrocytes. The blood count showed: erythrocytes, 3,750,000; leukocytes, 7,900; hemoglobin, 69 per cent (Sahli); neutrophils, 45 per cent; lymphocytes, 49 per cent and monocytes, 6 per cent. The temperature was 99.2 F., the pulse rate 100, and the respiratory rate 18 per minute. Physical examination showed a woman, 5 feet, 3 inches in height, weighing 109¼ pounds (49.5 Kg.). The surface area was estimated as 1.5 square meters and the basal requirement as 1,300 calories per day. The shape and configuration of the body were normal and in no way suggested polyglandular disease. She could stand with difficulty because of weakness. The entire body was pigmented, resembling somewhat the tint of ordinary seashore tan, but more nearly that shown in the illustrations at the end of Addison's monograph.[6] The face and dorsal aspect of the hands were somewhat darker than the rest of the body, but no part was free from pigmentation. The buccal mucous mem-

6. Addison, T.: On Disease of the Suprarenal Capsules, London, 1855.

brane was not pigmented (such lack of pigmentation is by no means uncommon in Addison's disease). The rectum and vagina were not examined. The brachial arteries were soft; a striking characteristic of the physical examination was the low tension of the radial pulse. The blood pressure was: systolic, 95; diastolic, 72. Examination was otherwise normal. Neither the liver nor the spleen was palpable. Each specimen of urine was tested (generally by the patient) for sugar and diacetic acid. Of 344 such tests made during her forty-seven days' stay in the hospital, sugar was present seventy-seven times and diacetic acid thirty-one times.

A noteworthy feature of the case, and one constituting a problem from the therapeutic standpoint, was the patient's peculiar response to insulin. She was so susceptible to this substance that she developed hypoglycemic symptoms on several occasions when 2, and even 1 unit more than her usual dosage was administered at midnight. On the other hand, glycosuria would occur on the slightest provocation, and if allowed to go unchecked was soon followed by vomiting and the appearance of diacetic acid in the urine. Hypoglycemia manifested itself first by mental dulness. If it occurred during sleep, she would be difficult to awaken, and after awakening would be slightly disoriented. If hypoglycemia occurred during the day, she would become mentally dull and forget-

*Blood Sugar Readings**

Date	Blood Sugar, Per Cent	Glycosuria	Insulin, Units	Food: Grams			Time
				Protein	Fat	Carbohydrate	
Oct. 27, 1925	0.342	+	25	4	9	10	Breakfast
	0.077	—	0	15	19	10	Lunch
	0.082	..	5	22	28	14	Supper
	0.0309	—	0	0	0	10	Midnight
Oct. 29 and 30, 1925	0.063	—	10	22	28	14	Supper
	.....†	—	0	0	0	10	Two hours later
	0.071	..	5	0	0	0	2 a. m.
	0.139	—	15	4	9	10	Breakfast
	0.0304	—	0	15	19	10	Lunch

* Blood was taken before injection of insulin or meal; insulin was given twenty minutes before specified meals.

† Slight hypoglycemic symptoms.

ful. Although ordinarily bright and intelligent, she never learned to recognize hypoglycemia, and would eat her lump of sugar only when ordered to do so. That these symptoms were actually due to hypoglycemia was proved on a number of occasions by obtaining blood sugar readings of less than 0.04 per cent during such attacks. During this stay in the hospital thirty-two mild hypoglycemic reactions occurred, and twice she had severe reactions in which she became unconscious and was given epinephrine hydrochloride. On both occasions, consciousness returned before glucose could be given intravenously.

Many blood sugar determinations were made during her stay in the hospital, the readings secured ranging from 0.423 to 0.03 per cent. The figures for two series of such determinations covering twenty-four hours each are shown in the table.

A regimen was finally evolved on which she gained weight, and remained sugar-free, shock-free and ketone-free. It consisted in a daily allowance of 57 Gm. of protein, 187 Gm. of fat and 57 Gm. of carbohydrate (2,139 calories a day), with 10 units of insulin twenty minutes before breakfast, 5 units twenty minutes before supper and 5 units at 3 a. m. On following this schedule, she went home, able to walk and feeling greatly improved.

Second Admission to Hospital.—On Jan. 15, 1926, she again returned to the hospital, this time because of extreme weakness. Her blood sugar was 0.193 per cent, the blood urea nitrogen 24 mg. per hundred cubic centimeters of blood and the carbon dioxide content of the plasma 51 per cent by volume. Fifteen

grams of sugar was excreted in the urine in twenty-four hours. Acetone was present in the urine, but no diacetic acid. The blood count showed: erythrocytes, 4,800,000; leukocytes, 13,000; hemoglobin, 86 per cent (Sahli); neutrophils, 46 per cent; lymphocytes, 47 per cent; monocytes, 2 per cent, and eosinophils 5 per cent. Results of physical examination were essentially the same as on the previous admission except that the patient was weaker than before, and that the pigmentation had become noticeably deeper. The blood pressure varied from 90 systolic and 66 diastolic to 78 systolic and 55 diastolic, showing little variation attributable to meals or injections of insulin; 30 mg. of ephedrine[7] taken by mouth also failed to raise the blood pressure. The pulse rate varied from 80 to 108 and respirations from 17 to 20 per minute. The temperature was subnormal. Vomiting commenced on January 17. She grew weaker; diacetic acid as well as acetone appeared in the urine. Two days later, cough and pain in the chest appeared. At 6 a. m., January 20, she complained of difficulty in breathing and severe pain in the chest. She became unconscious and died suddenly.

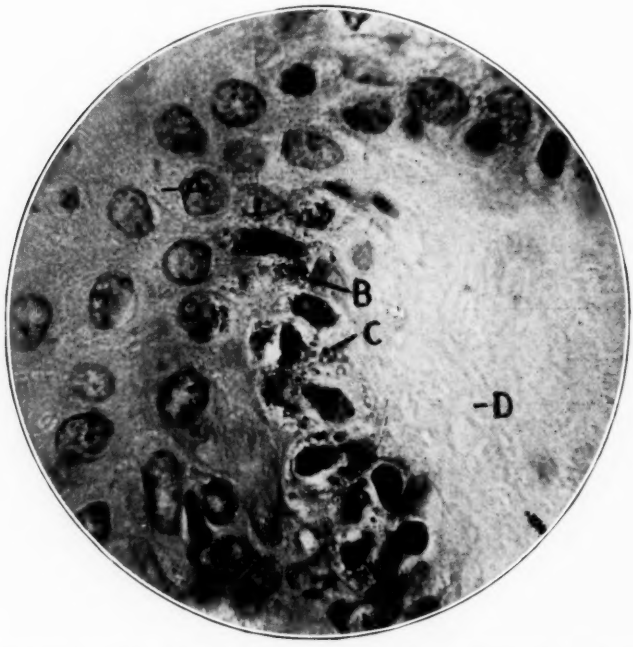
Autopsy.—This was performed five and one-half hours after death by Dr. Morton McCutcheon, assistant professor of pathology. Interest centered chiefly in the suprarenal glands: a prolonged search by Dr. McCutcheon and others failed to reveal the slightest trace of the suprarenal gland on the right side; one piece of tissue was removed on suspicion, but on section it exhibited no semblance of suprarenal structure. The suprarenal gland on the left side was readily found and measured 15 by 35 by 5 mm.; the cortex was white; the medulla was mottled pink and gray; its appearance did not suggest tuberculosis. On microscopic examination, it showed a normal capsule; there was, however, a marked increase in connective tissue, the latter being of adult type chiefly. Lymphocytic infiltration was extensive; due to these changes, the architecture of the gland was indistinct, and in most parts the cortical cells were small and devoid of lipoid. Islands of large cells were found at the periphery; these also were devoid of lipoid.

The anatomic observations in the other organs were as follows: the pancreas weighed 60 Gm. and measured 20.5 by 3 by 1.5 cm.; it was not pigmented or fibrotic as in hemochromatosis, but flaccid and normally lobulated. The liver also was normal in consistency and without any sign of cirrhosis. It weighed 1,360 Gm., and its capsule was transparent; on section it was dark brown and showed indistinct nutmeg markings. The gallbladder and bile ducts were normal. The pleural cavities were free from fluid or adhesions, and the pericardial sac was normal. The heart weighed 230 Gm., the epicardium was smooth, and the myocardium dark brown; slight thickening of the mitral valve was present. Culture of the heart blood showed *Bacillus coli communis*. The lungs were pale and somewhat watery on section, otherwise normal. The stomach, esophagus and intestines were normal. The spleen weighed 120 Gm., was of normal consistency and on section showed normal color and markings; its capsule was not thickened. The kidneys weighed 140 Gm. each and were of normal consistency; on section, the left kidney was congested, the right pale. Both ureters were normal, as were also the internal and external genitalia.

On microscopic examination, the pancreas showed a slight increase in the interlobular fibrous tissue; no pigments were present; both acini and islets appeared somewhat smaller than usual, and the latter were numerous and contained some small, poorly staining cells and also some large cells with deeply staining nuclei. The liver capsule and interlobular structures were normal; the liver cells appeared swollen and rarefied, with nuclei swollen or poorly staining. These changes were less marked toward the periphery of the organ, the cells in the vicinity of the capsule often appearing normal; greenish-brown pigment of finely granular character was found rather abundantly, chiefly in the hepatic cells of the central lobular region. This pigment did not react for iron; Kupffer cells were not conspicuous, and there was no evidence of hepatic cirrhosis. The cap-

7. Miller, T. G.: Am. J. M. Sc. **170**:157 (Aug.) 1925.

sule of the spleen was not thickened, and the trabeculae were normal; the splenic follicles were numerous and slightly enlarged. The only noteworthy change in the kidneys was an increase in the interstitial tissue of the subscapular region, associated with lymphatic infiltration. The sections of the lung were essentially negative. In the thyroid the interstitial tissue was normal; the acini varied considerably in size and were filled with colloid; hyperplastic changes were not present. A section of the skin of the abdomen (fig. 1) showed marked pigmentation of the stratum germinativum comparable to that found in negroes. The pigment did not give a reaction for iron.



Abundant deposition within the skin of large pigment granules which gave a negative reaction for iron. *A* indicates the stratum germinativum; *B* and *C*, pigment granules; *D*, corium.

COMMENT

Bronzed diabetes must of course be considered here as a possible explanation for the pigmentation and glycosuria. This disease, known since von Recklinghausen's [8] time as hemochromatosis with glycosuria, and before this as the cirrhose hypertrophique pigmentaire of Hanot and Chauffard,[9] is characterized by cirrhosis of the liver, sclerosis of the pancreas and other organs and the presence of a pigment reacting to iron,

8. Von Recklinghausen: Tageblatt der 62. Versammlung Deutscher Naturforscher und Aerzte in Heidelberg, 1889, p. 324.

9. Hanot, V., and Chauffard, A.: Rev. de méd. **2**:385, 1882.

none of which this case exhibited. On the other hand, in addition to presenting the characteristic clinical and chemical picture of diabetes mellitus, the pigmentation, vomiting, excessive hypotension and asthenia in this case presented an unmistakable picture of Addison's disease.

The pathologic observations pointed to an old inflammatory process involving both the islands of Langerhans and the suprarenal glands, with evidences of attempts at regeneration in [10] both. The etiology of this process remains obscure. From the history it would appear that the involvement of these two structures occurred simultaneously, and this view was confirmed at autopsy.

The hypersensitivity to insulin which this patient manifested to an increasing extent, especially during the last weeks of her life, can best be explained on the basis of diminished suprarenal function. That such hypersensitivity may be caused by suprarenal insufficiency is proved by the fact that the administration of insulin to suprarenalectomized animals,[11] or to persons with Addison's disease, is known to produce hypoglycemia out of all proportion to that which occurs when the suprarenals are functioning normally. For example, Marañon [12] reports the case of a woman, aged 40, with Addison's disease, who suffered severe hypoglycemic symptoms following the administration of 10 units of insulin hypodermically, while in another case of Addison's disease occurring in a girl of 16, death followed the administration of 5 units of insulin.

Of especial interest to the student of endocrinology is the fact that in this case there was an insufficiency of two "antagonistic" glands, namely the islands of Langerhans and the suprarenals. This so-called antagonism refers to the glycemic action of the two respective hormones, and finds its practical application in the use of epinephrine hydrochloride in insulin shock. This usage is based on the fact that the hypodermic injection of epinephrine raises [13] while insulin lowers [14] the blood sugar. On the other hand, when an insufficiency of these hormones is present, the opposite state of affairs exists; namely, in suprarenal insufficiency (Addison's disease) the blood sugar is low,[15] while in insufficiency of the islands of Langerhans (diabetes) the blood sugar is high. Based on these considerations, destructive radiation of the suprarenal glands has

10. Boyd, G., and Robinson, W. L.: Am. J. Path. **1**:135 (March) 1925. Warren, S., and Root, H. F.: Ibid **1**:415 (July) 1925.

11. Hallion, L., and Gayet, R.: Compt. rend. Soc. de biol. **92**:945 (April 3) 1925. Sundberg, C. G.: Ibid **89**:807 (Oct.) 1923.

12. Marañon, G.: Presse méd. **33**:1665 (Dec. 19) 1925.

13. Blum, F.: Deutsches Arch. f. klin. Med. **71**:146 (Oct.) 1901.

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been practiced in the treatment of diabetes mellitus.[16] The published data, nevertheless, do not indicate any striking results either in curing the diabetes or in producing Addison's disease. Judging, however, from the clinical course of the case here reported, the destruction of the suprarenal glands by any agency could scarcely be regarded as a safe or desirable form of treatment for diabetes mellitus.

SUMMARY

The combination of Addison's disease and diabetes mellitus is extremely rare. It is moreover of great interest, because the two ductless glands involved, namely, the suprarenals and the islands of Langerhans, secrete hormones producing opposite glycemic effects. The case herewith reported presented both the clinical and chemical evidences of diabetes mellitus, together with the pigmentation, asthenia, low blood pressure and vomiting which are characteristic of Addison's disease. Autopsy bore out this diagnosis. Unusual therapeutic difficulties were encountered owing to the existence of a hypersensitivity to insulin and a marked tendency to ketosis, the former no doubt being due to suprarenal insufficiency.

16. Dresel, K.: Deutsche med. Wchnschr. **46**:1240 (Nov. 4) 1920. Beumer, H.: Ibid **47**:369 (March 31) 1921.

CONGENITAL VENTRICULAR SEPTAL DEFECT IN A MAN, AGED SEVENTY-NINE*

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Ventricular septal defects are usually situated just beneath the aortic cusps, anterior to the undefended space, and are frequently associated with other anomalies, such as pulmonary stenosis and dextroposition of the aorta. Rarely do they occur alone. The following case is unique in the peculiar location and large size of a congenital ventricular septal defect unassociated with other anomalies. The age of the patient and the absence of cardiac symptoms other than a terminal cyanosis are additional features of interest.

REPORT OF CASE

History.—H. F., a white man, aged 79, an inmate of the Old Folks Home of the Jewish Hospital, whose chief complaint was stomach trouble, was admitted to the medical ward in the service of Dr. S. Solis Cohen, May 4, 1926. His family history was unimportant. At the age of 40 he had had typhoid fever, and at the age of 64 he had dislocated his right knee joint; the dislocation had persisted, making it necessary for the patient to use crutches. For twenty years he had suffered from severe shooting pains down the thighs and legs posteriorly; these pains occurred in attacks which lasted for two or three days at a time. Other than the aforementioned difficulties, the patient had been in good condition and had felt well until about two and one half weeks before his admission to the hospital. At this time an attack of sciatica occurred, accompanied by nausea, which caused the patient to vomit on several occasions. He never had had shortness of breath, swelling of the legs, palpitation or cardiac pain. On admission to the hospital his temperature was normal; the pulse rate varied between 80 and 90, and his respiration was normal.

Physical Examination.—This showed an aged white man, fairly well nourished, lying quietly in bed, with marked cyanosis of the hands and feet. There was some engorgement of the veins of the neck, and examination of the heart revealed striking signs. At the ensiform cartilage there was an intense systolic thrill, and a loud, harsh systolic murmur. The murmur could be heard all over the cardia, but was loudest at the ensiform cartilage. The aortic and pulmonic second sounds were not accentuated. It was difficult to outline the heart borders, but there did not seem to be an enlargement either to the right or to the left. Examination of the abdomen showed the liver edge palpable two fingerbreadths below the costal margin, but it was not tender. The spleen was not palpable; evidence of ascites was not found. Examination of the extremities showed the old dislocation of the right knee, and, as mentioned in the foregoing, marked cyanosis of the hands and feet.

Diagnosis.—At first sight this seemed to be either a tricuspid or a mitral lesion, but the history did not denote mitral disease; the aforementioned murmur and thrill were the only indications of this form of valvular disturbance. Against a tricuspid lesion sufficiently severe to produce such pronounced physical signs, was the absence of the phenomena of failure of the right side of the heart; edema was not present, nor was there marked enlargement of the liver—the clinical picture was not that of congestive heart failure.

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The unusual position of the intense thrill and the harsh quality of the murmur, together with the peculiar cyanosis, suggested the possibility of a latent congenital lesion, such as a septal defect; this was the probable diagnosis made, but it was not possible to say whether the defect was between the auricles or between the ventricles.

The course of the illness was steadily downward. The patient developed urinary retention, finally refused to take food and died on May 31. He did not show signs at any time of congestive heart failure. Urinalyses had consistently shown heavy traces of albumin, white blood cells and occasional hyaline casts. The blood count showed a moderate degree of anemia, with 20,000 leukocytes, 80 per cent of which were polymorphonuclear neutrophils. The blood pressure was systolic, 100; diastolic, 80, and remained at about this level. The blood Wassermann reaction was negative. At the time of admis-

Fig. 1.—Congenital ventricular septal defect situated in the posterior half of the septum, midway between the apex and the mitral orifice. There were not any associated anomalies.

sion, the blood urea nitrogen was 90 mg., which was ascribed to the urinary retention. With forced fluids and catheterization, it dropped to 23 mg.

The electrocardiogram, taken two days after admission, showed a rate of 84, irregular from auricular premature beats. The auriculoventricular bundle conduction was normal. The right branch bundle conduction was impaired, with delay. There was evidence of right ventricular preponderance and myocardial degeneration.

Autopsy.—Postmortem interest was centered in the heart. Other than marked sclerosis of the kidney and chronic cholecystitis, there was nothing unusual about the appearance of the other organs.

The heart weighed 370 Gm. and appeared normal in size. The surface of the visceral pericardium was somewhat roughened with fine shreds of fibrin, representing a terminal fibrinous pericarditis. The muscle of the left ventricle was

1.5 cm. in thickness, firm in consistency and showed minute patches of fibrous tissue. The muscle of the right ventricle was 0.4 cm. in thickness. The right side of the heart appeared somewhat dilated, containing blood clot. The tricuspid orifice was 13 cm. in circumference; the valve cusps appeared normal. The pulmonary orifice was 8.5 cm. in circumference; these cusps were likewise normal. The aortic orifice was 9 cm. in circumference; the aortic leaflets were somewhat thickened and sclerotic, and the aortic arch, with the exception of the first portion, was markedly sclerotic. The openings of the coronary arteries were somewhat narrowed, and the coronary vessels throughout their course were generally thickened. The mitral orifice was 10 cm. in circumference; the cusps were slightly thickened, and there was a large atheromatous plaque in the posterior leaflet.

The striking feature of the heart was the large defect of the interventricular septum situated in the posterior half of the septum, about midway between the

Fig. 2.—Right side of the heart showing openings of septal defect between the muscle columns near the apex. White rods are passed through two of the openings.

apex of the left ventricle and the mitral ring (fig. 1). The defect was circular in outline, measuring 2 cm. in diameter, and communicated with the right ventricle near the apex by means of an aneurysmal pouch with fenestrated openings. This pouch was 2.5 cm. in depth, and was large enough to accommodate a good sized olive. The edge of the defect on the left side of the heart was fibrous and smooth. The openings in the right ventricle were four or five in number, occurring between the columna carneae near the apex of the right ventricle (fig. 2). Directly above the defect and just below the mitral orifice was a roughened spot where thrombus material was attached.

The location of the defect, its large size, the smooth, fibrous edge, the aneurysmal communication with the right ventricle and the natural openings between the muscle columns near the apex of the right ventricle were features which distinguished this as a congenital lesion.

COMMENT

Ventricular septal defects belong to that group of cardiac anomalies which are unassociated with cyanosis, except as a transient or terminal event. Comprising this group are patent ductus arteriosus, direct communications between the aorta and the pulmonary artery, defects of the auricular septum and defects of the ventricular septum. With any such anomaly, I believe, from morphologic evidence, that the flow of blood is from the side in which the pressure is higher, that is, systemic circulation, into the side in which the pressure is lower, or the lesser circulation. In other words, the flow of blood is from the left to the right, or what has been termed by Abbott [1] as arteriovenous shunt. Under such circumstances there is not a cause for cyanosis, and the only pathologic factor at work is a slowly developing strain, manifested by hypertrophy of the walls and by fibrosis in the region of the defect. If, because of heightened tension on the pulmonary side, or weakening of the systemic circulation, a reversal of the shunt occurs, that is, the blood flow is from the venous to the arterial side instead of from the arterial to the venous, cyanosis occurs; this may be transient or terminal, constituting what the French have termed "cyanose tardive."

It is probable that such was the case in the present instance. All through life the defect did not interfere in any way with good cardiac function; the shunt of blood was probably from the left to the right. During the last days of life it is probable that a reversal of the shunt occurred sufficient to produce cyanosis.

The diagnosis of cardiac defects belonging to this so-called noncyanotic group usually does not offer any great difficulty. The presence of striking physical signs and the absence of cardiac symptoms are characteristic features. A peculiar harsh murmur of unusual rhythm and intensity, often accompanied by a thrill, situated to the left of the sternum in the first or second interspace, or over the middle of the precordium, and in many instances associated with evidences of dilatation of the pulmonary artery, are the most important diagnostic features of this noncyanotic group. Such physical signs in a person without a history of rheumatic fever or other illnesses commonly causing endocarditis, readily permit a diagnosis of a congenital defect belonging to this group.

The problem, then, is to differentiate the type of lesion, and this is often possible, depending on the distinctive physical signs of the various defects.[2]

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1. Abbott, M. E., and Dawson, W. T.: The Clinical Classification of Congenital Cardiac Disease, Internat. Clin. **4**:155, 1924.

2. Abbott and Dawson (footnote 1). Weiss, Edward: The Differential Diagnosis of Congenital Heart Disease, M. Clin. N. Am., Philadelphia number **10**:185 (July) 1926.

In the case under discussion, the advanced age of the patient seemingly was against a congenital lesion, but the distinctive quality and unusual position of the harsh murmur and intense thrill, without the history or physical indications of an acquired lesion, and without evidence of congestive heart failure, led to the conclusion that in this case the lesion was congenital, probably a septal defect. Whether this defect was between the auricles or between the ventricles, the location of the murmur and thrill did not permit us to say. The further conclusion that a right to left (terminal) shunt had occurred, and that the flow of blood through the defect was probably from the venous to the arterial side could be drawn from the presence of a peculiar deep cyanosis of the hands and feet.

Perhaps the most interesting feature of this case report is the rarity of the type of defect. As mentioned before, defects of the ventricular septum usually occur at the base and are readily explained on the basis of an arrest of development, particularly in their common association with other anomalies of the pulmonary conus and great vessels.

The defect under discussion occurred in an extraordinary position, and I am unable to find any recorded similar cases, in which such a large defect occurred in this location unassociated with other anomalies. Dr. Abbott,[3] whose knowledge of the subject of cardiac anomalies is authoritative, states that the present case is unique. She suggests in explanation of its formation that, from a comparative standpoint, a homologue can be found in the heart of the python, in which a communication exists low in the septum between the dorsal and ventral ventricles.[4]

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3. Personal communication to the author.

4. Abbott, M. E., and Stanley, Elanor: Cardiac Defects in the Light of the Comparative Anatomy of the Vertebrate Heart, Bull. Internat. A. M. Museums 8, **1**:32 (Dec.) 1922.

SOME CONDITIONS AFFECTING SUBJECTIVE AND OBJECTIVE MANIFESTATIONS OF HUNGER*

HUNGER SENSATION GIVING RISE TO A MARKED RESPIRATORY CHANGE

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AND
NATHANIEL KLEITMAN
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While making simultaneous observations on gastric motility (by the balloon method) and on the basal metabolic rate (Kleitman),[1] a striking increase in the respiratory rate was manifested during some periods of gastric hunger contractions (fig. 1). The increase was recognized by the subject (F. H.) as accounting for his previous belief that the metabolic rate was increased with hunger contractions. This belief occasioned the investigation but was based mainly on subjective experience, particularly during a thirty-three day fast undertaken some time previously. However, similar subjective experience during earlier fasts had already led to a study of this problem by Dr. Kunde (unpublished work). She made observations on a number of subjects, but did not obtain conclusive evidence of an increase in the basal metabolic rate with increases in gastric motor activity. This observation was confirmed by Kleitman. Kunde, however, did not note the striking increase in the respiratory rate which we observed, although she found that minor and irregular changes in respiration occurred. None of Kunde's subjects fasted more than five days during her study, while our own investigation did not begin until the twenty-third day of a forty-one day fast.

The fact that neither Kunde's nor Kleitman's study revealed an increase in the basal metabolic rate during periods of hunger contractions indicates that the increased respiratory rate was not due to greater need of oxygen. Apparently, it was reflexly induced by the hunger sensation. The increase in the respiratory rate was accompanied by a simultaneous decrease in the depth of the respiratory excursions. Whether the increase in rate or the decrease in depth was primary is an unsettled question. If it were the latter, this phenomenon would be comparable to the reflex rigidity of the abdominal muscles which is frequently manifested with intra-abdominal lesions. But, instead of the abdominal muscles contracting, the contractions of these muscles and of the diaphragm seemed to be inhibited. That is, an increase in intra-abdominal pressure apparently was reflexly prevented to avoid an

* From the Hull Physiological Laboratory of the University of Chicago.

1. Kleitman, N.: Am. J. Physiol. **77**:233, 1926.

Fig. 1.—Graphic records of basal metabolic rate in three successive ten minute periods, showing increased respiratory rate (*I*) during period of gastric hunger contractions.

increase in the hunger pain. However, as it was not the change in depth but rather the increase in the respiratory rate which was most obvious, this increase will chiefly be referred to, for descriptive purposes, in what follows.

Occasionally, the metabolic graphs showed a considerably increased respiratory rate somewhat independent of the individual hunger contractions, and also at times when the subject thought that his rate had been normal. This raised the question as to whether we were not dealing with an artefact caused by the construction of the metabolic apparatus. At least, it seemed possible that a change in the type of respiration might be reflected as an increase in the rate because of the interference with natural breathing occasioned by the apparatus. For instance, the gas exchange in the apparatus used (Sanborn-Benedict type) occurs about

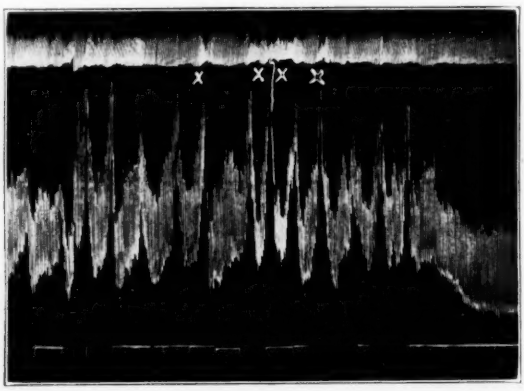

Fig. 2.—Period of gastric hunger contractions (middle tracing). The upper tracing is a pneumograph record showing intermittent increases in respiratory rate (*X, X, X*); time is given in minutes below.

10 cm. from the subject's mouth. This makes an increased dead space which, while perhaps of no consequence under normal conditions, might have to be taken into consideration when respiration is altered, during fasting, undernutrition and other conditions. Observations were therefore made (after the forty-one day fast) without the metabolic apparatus, using a pneumograph, tied around the abdomen, in its place. Increases in the respiratory rate nevertheless occurred, but the increases were not, as a rule, so continuous (fig. 2) as they appeared on the metabolic graphs (fig. 1). The increases also agreed better with subjective sensations. Observations were also made without the balloon in the stomach and without the pneumograph, and again, although naturally with some difficulty, it was possible to recognize distinct increases in the respiratory rate on some occasions while subjectively experiencing hunger sensations.

This respiratory reflex had not been observed in the extensive work of Carlson [2] on hunger. It seemed possible to explain this at first by the fact that the curves of the gastric contractions tend to obscure the rate of respiration on the usual graphs. That is, a simultaneous independent record of respiration with the pneumograph or metabolic apparatus seemed necessary to bring this phenomenon to light. However, Carlson had used such methods in his investigations, and in our study it became clear before long that the condition of the subject, rather than the mode of observation, determined the results. In this connection, it is interesting to note that the subject (F. H.) failed to recognize the increased respiratory rates before our objective evidence was obtained—this, in spite of the fact that he had, at different times, fasted a total period of about three hundred and fifty days before the present experiment. That, among other things, argues against the possibility that the respiratory changes were caused by conscious attention to breathing. During most of the longer fasts, F. H. experienced "air hunger," which was attributed to acidosis. It seems possible, however, that the "air hunger" was the respiratory reflex which may, at the same time, have been accompanied by some degree of true air hunger incident to acidosis. The belief that the basal metabolic rate was increased with the periodic contractions, nevertheless, did not rest on the experience of air hunger during fasting, but was more directly based on the experience of considerable restlessness during some hunger periods.

As indicated in figure 2, the respiratory increases were usually intermittent. Respiration increased synchronously with a specific type of hunger sensation which often paralleled, but was sometimes more or less independent of, the gastric hunger contractions. With this sensation, an increased sense of tension in the gastric region was generally thought to be felt, but increases in neither the gastric tonus nor gastric contractions could account for it. This and other evidence indicated that the sensation must have come from a site beyond the position of the balloon if, indeed, it was at all caused by contractions or increases in tonus. The lack of a direct relation between the gastric contractions and the hunger sensation with the change in the respiratory rate was emphasized when the phenomenon gradually disappeared by the end of the fourth month after the forty-one day fast. About this time, the gastric periods became somewhat less frequent, but no other change, either in gastric tonus or contractions, could account for the disappearance of the sensation with the peculiar respiratory responses.

We then attempted to reestablish this hunger sensation, as we wished to study its manifestations further. F. H. had increased his carbohydrate intake a little about the time that the increases in the res-

2. Carlson, A. J.: Am. J. Physiol. **31**:151, 1912; ibid. **31**:175, 1913; The Control of Hunger in Health and Disease, Chicago, 1916.

piratory rate became less prominent. Moreover, it was thought that acidosis or carbohydrate deficiency during fasting might have initiated the phenomenon by affecting the respiratory center. Hence, it was believed that the reflex would again become evident with carbohydrate restriction while the protein intake was kept practically constant. This, however, did not prove to be the case, even when some meals did not contain any carbohydrate and when the hunger contractions were more intense than usual. After that the effect of the use of liberal quantities of carbohydrate was observed. The respiratory rate was then found to be even less inclined to increase than with carbohydrate restriction. It should be said here that a small (from 10 to 25 per cent) increase in the respiratory rate was nearly always observed during periods of hunger contractions, but the increase which we accepted as evidence of the specific hunger sensation was an increase of about 100 per cent or more; it was sometimes as high as 200 per cent.

Since we had failed to reestablish the hunger sensation with the change in the respiratory rate by altering the carbohydrate and fat ratio in the diet, our attention was directed to the protein intake. The proportion of protein used was not considered in the first instance, because wide variations had been made previously without any obvious effect on the respiratory reflex. About the time that the evidence of the respiratory increase disappeared, a more or less constant and slightly high protein intake had been instituted. Protein was therefore reduced to create a degree of protein starvation (from 15 to 25 Gm. daily being used), while other food was kept adequate. Within two days the hunger sensation with the accompanying respiratory reflex showed signs of returning; that is, when hunger sensations developed, the subject felt as if they would presently "take the breath away," although objective evidence did not indicate that. After three more days, however, increases in the respiratory rate became evident on the graphs; these increases had been absent for a month and had occurred clearly only once during the preceding two months. These results again show that the peculiar hunger sensations and the respiratory changes were not produced by conscious attention, for they did not return when they were most expected—with carbohydrate restriction. The surprisingly quick effect of protein restriction at this time was probably due to the fact that a partial decrease in the protein intake preceded the more rigid restriction. Notwithstanding the previous inability of the subject to recognize clearly the circumstances under which the hunger sensation with the respiratory increase arose, it now became evident that this sensation invariably developed with protein starvation. Its manifestation during a few short periods of excessive protein intake, within the first four months after the forty-one day fast, had somewhat obscured the relationship; with the prefasting conditions apparently restored,

however, the subject realized that it was this hunger sensation which always made prolonged protein restriction, beyond a certain point, practically intolerable. This became clearer with further experimentation, for it was then found that, after the fourteenth day of protein restriction, this hunger sensation was also manifested during motor quiescence of the empty stomach and even during digestion (fig. 3). The sensation, nevertheless, was usually more distinct during the periods of hunger contractions than at other times.

Some of the observations were so unexpected that the question arose as to whether anticipation of the sensation might not, at least in some instances, give rise to the increases in the respiratory rate. As a result of some tests, it proved possible to reproduce brief respiratory increases by imagining the conditions under which they occurred and adjusting

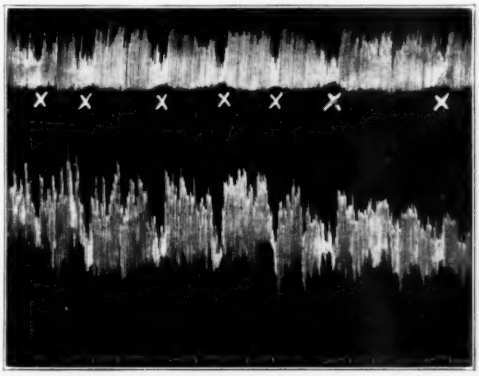

Fig. 3.—Record of gastric motility (middle tracing) during digestion of first protein meal after twenty-four days of protein restriction—beginning thirty-five minutes after ingestion of 225 Gm. of roast veal. Upper tracing is a respiratory record with unusually persistent intermittent increases in rate (*X, X, X*) synchronous with hunger sensations; lower tracing, time in minutes.

the breathing accordingly. This, however, required distinct effort and a close attention to detail, neither of which was noticeably involved in the natural manifestation. On the other hand, it was more difficult to breathe normally (at a slow rate) when a strong sensation occurred than it was to imitate the rapid breathing. Difficulty in preventing the increase in the respiratory rate might therefore, in a measure, serve as a check test. Another question investigated was whether the respiratory increase would be manifested during sleep. The necessary experimentation proved difficult, but such results as seemed dependable warrant the conclusion that the respiratory rate was not affected during sound sleep, and that respiratory irregularities might be taken as an index of light or dreamy sleep or of a transition between sleep and wakefulness.

Before F. H. more permanently discontinued the protein restriction which was necessary to prevent the hunger sensation with the respiratory increase from disappearing, attempts were made to determine in what particular respects this sensation could be distinguished subjectively from the ordinary hunger sensation which has little if any effect on the respiratory rate. Serious difficulties were encountered here, first, because a hunger sensation of the type which when strong gave rise to objective evidence of an increase in the respiratory rate, did not yield such evidence when the sensation was mild or of brief duration; second, because the hunger sensation with the change in the respiratory rate was frequently synchronous with the gastric contractions, and third, because some gastric contractions (of F. H. as well as of another subject) were recorded which did not cause any sensation. The complexity of the situation easily explains why it has not been possible to discover the hunger sensation with the increase in the respiratory rate by subjective experience alone. Nevertheless, repeated observation, with the assistance of objective methods and under wide variations in conditions, made it certain that the hunger sensation with the respiratory reflex differs from the ordinary hunger sensation more in a qualitative than in a quantitatve way. Besides being more diffuse or more irradiating, the hunger sensation with the change in the respiratory rate was less sharply defined in its onset and abatement than the ordinary hunger sensation which is referred more or less directly to the gastric contractions. In this respect, it was somewhat similar to sensation accompanying increases in gastric tonus. At the onset of sensation, this similarity usually gave the impression that a strong gastric contraction was about to take place, but neither contraction nor tonus increase necessarily followed. A sensation caused by tonus variations alone was always milder and less diffuse than the hunger sensation with the respiratory increase. Besides this, the ordinary hunger sensation often impressed F. H. as being simply a reminder of a state of emptiness which could be remedied by ingesting some nonnutritive material, while the hunger sensation with the respiratory reflex appeared to be a more direct call for nourishing food. It might be described as a famishing sensation or as hunger with a keen appetite. However, it should be emphasized that the two sensations had a common element in that both involved a desire to ingest "something," and it is evidently this common element, rather than the peculiarities of the individual sensations, that forces itself most on consciousness.

THE RÔLE OF GASTRIC ACIDITY IN THE HUNGER COMPLEX

Boring[3] reported that the introduction of 5 or 10 per cent hydrochloric acid into the stomach produced a sensation of hunger. Carlson,[2]

3. Boring, E. G.: Am. J. Psychol. **26**:1, 1915.

using 0.5 per cent hydrochloric acid, found that it gave rise to an appetite-like sensation. A relation between gastric acidity and the intensity of the desire to eat was also noted by one of us in connection with previous studies (Hoelzel [4]). This relationship was observed to hold for variations in the gastric acidity which occurred naturally (before prolonged fasting was undertaken) as well as for artificial modifications. The artificial changes were made by adding a small amount of a strong solution of hydrochloric acid or sodium hydroxide to the aspirated gastric residuum and then returning it to the stomach. In these tests, the acidity was always kept within natural limits (0 to 0.5 per cent free hydrochloric acid), and the volume of the residuum remained practically unchanged, because a little was used for titration before and after the hydrochloric acid or sodium hydroxide was added. It could not be settled by these more or less preliminary tests whether hunger or appetite was modified.

The relation between the gastric acidity and the intensity of the desire to eat observed before was obscured during prolonged fasting and during the first four months after fasting. The desire to eat was then often as keen with the acidity relatively low as it had been previously with high acidity. Nevertheless, when considered separately, the effect of variations in gastric acidity was also indicated in certain ways during this period. Thus, with the acidity relatively higher, the desire to eat was more intense during the last half of the thirty-three day fast than during the last half of the subsequent forty-one day fast. During the first four months after fasting, it was also noticed that the amount of protein which was relished or which could be tolerated depended largely on the available hydrochloric acid secretion (Hoelzel [4]). The effect of gastric acidity on the general desire to eat was, however, complicated during this period by at least one other factor, namely, increased gastrointestinal sensibility; this will be discussed more fully in the next section.

It will be recalled that the hunger sensation with the increase in the respiratory rate was observed for the first time during the latter part of the forty-one day fast. The average gastric acidity was then relatively low. During the first four months after the fast, this sensation was observed with both high and low acidity. On the basis of this experience alone, a relationship between this hunger sensation and gastric acidity was not indicated. However, as suggested in the foregoing, the relationship may have been obscured during this period because of increased sensibility and other factors. That this was the case became evident later when the prefasting state of nutrition and more normal sensibility had apparently been restored. Then the hunger sensation with the respiratory reflex disappeared and remained absent for about two months, during which the average or potential gastric acidity was kept

4. Hoelzel, F.: Am. J. Physiol. **73**:463, 1925; ibid. **77**:166, 1926.

low with a moderately high protein intake, and it again returned with protein restriction which increased the acidity. We have already mentioned that the return of the hunger sensation with the change in the respiratory rate at this time showed that this sensation had always developed with protein starvation; as the acidity was incidentally increased with the protein restriction, it also became evident that this hunger sensation was the basis of the increased desire to eat which had previously been attributed to the higher acidity. Later, the relationship between gastric acidity and the hunger sensation with the increase in the respiratory rate was also demonstrated during digestion as the sensation developed most clearly with the first protein meal after a period of protein restriction—that is, at a time when the digestive acidity would be expected to be highest (fig. 3).

This observed relationship between gastric acidity, the peculiar hunger sensation and the increase in the respiratory rate was tested further. First, the spontaneous or natural appearance of the sensation was suppressed by lowering the potential gastric acidity with a high protein intake. Then, after the gastric residuum was removed, from 10 to 25 cc. of 0.5 per cent hydrochloric acid was introduced into the stomach (by tube) to determine whether the acid would cause the hunger sensation. Water was used for control. A brief sensation usually developed within from one to four minutes after the introduction of the acid, and the sensation generally recurred a few times before the effect of the acid had disappeared entirely. By that time the acidity was also considerably reduced. With the repeated introduction of fresh acid, the effect gradually became less pronounced or was obscured by the development of a mild continuous burning sensation which, however, did not materially affect the rate of respiration. Moreover, the effect of the acid became more vague as time elapsed after the spontaneous appearance of the sensation had been suppressed. Water did not cause the peculiar hunger sensation. Two tenths per cent hydrochloric acid yielded inconclusive results. On one occasion, a sensory response occurred immediately or while the (0.5 per cent) acid was still being introduced. The tip of the tube, in this instance, was thought to have been drawn well into the antrum by gastric motility.

The foregoing observations and the fact that the hunger sensation was often preceded by an increase in gastric tonus or contraction seemed to indicate that the acid became effective on passing into the duodenum. Accordingly, a number of tests were made by introducing about 10 cc. of 0.5 per cent hydrochloric acid, by tube, directly into the duodenum and again using water for control. In these tests, the position of the tube was determined mainly by the character of the aspirate. The subject (F. H.) was unaware as to whether hydrochloric acid or water was introduced as the observer (N. K.) selected and introduced the test fluids in irreg-

ular order and with adequate time intervals between the individual tests. A sensory response was not always elicited by the hydrochloric acid. This might have been caused by neutralization of the acid or by failure to reach a specific site or sufficient area in which the acid might have been effective. The sensation was not manifested clearly more than once after any given injection, and then the latent period was usually shorter than when acid was introduced into the stomach. Most of the tests were made with the tube kept in one position—with the tip apparently from 5 to 15 cm. beyond the pylorus (as inferred by the length of the tubing swallowed). In one test, however, the tube was permitted to pass well into the duodenum, and then acid was introduced at various intervals while the tube was being gradually drawn back. When the tube was well in, the results were not uniform. When the tip of the tube appeared to have been at the pylorus, an immediate sensory response to the acid occurred. When the tube was pulled back a little farther, the aspirate showed that the tip was back in the stomach.

The relative consistency of the results with hydrochloric acid was, however, upset by the observation that water introduced into the duodenum, also gave rise, at times, to the hunger sensation with an increase in the respiratory rate. This was unexpected, and led to the previously mentioned tests concerning the effect of anticipating the involved hunger sensation. Anticipation may have intensified some of the respiratory changes, but deliberate attempts to avoid increases in the respiratory rate indicated more definitely that water sometimes gave rise to the hunger sensation with the respiratory reflex or to a sensation which could not be distinguished from it. This does not mean that when water enters the duodenum normally by way of the stomach it can elicit the sensation. Natural conditions are not simulated when substances are introduced directly into the duodenum. The presence of even the tube alone introduces an abnormal factor. The first time that the tube was introduced, the subject felt some nausea and dizziness. The second time only dizziness was occasioned. After that, no sensation could be attributed directly to the presence of the tube alone, but its presence added to the introduction of water, regardless of whether or not the duodenum was at the moment naturally prepared to receive anything, may have given rise to sensation which would not occur normally. Nevertheless, evidence was obtained, without the use of the duodenal tube, that other substances besides hydrochloric acid might also elicit the hunger sensation with the increase in the respiratory rate. For instance, during a period of protein restriction, this sensation was manifested clearly while test meals made up chiefly of fat (butter) were being digested. Did the fat or fatty acid elicit the sensation, or did sufficient hydrochloric acid occasionally accumulate and give rise to the sensation even though a number of aspirated digestive fractions showed practically no free

acid? However, as the hunger sensation with the increase in the respiratory rate did not develop with similar fat meals after protein realimentation, altered sensibility may have played the major rôle in determining results.

In this connection, another observation is of interest. As mentioned in the foregoing, some nausea was occasioned by the presence of the tube in the duodenum for the first time. It was therefore thought that close observation might reveal a sensation as the tube passed through

TABLE 1.—*Showing Duodenal Regurgitation More Directly Increased with Protein Restriction than with Increased Gastric Acidity*

Date (1925)	Number of Aspirations§	Average per Cent Free Hydrochloric Acid	Approximate per Cent Bile Contamination*	Preceding Regimen †
Oct. 5	7	0.050	15	After liberal diet with about 3.6 Kg. meat
6	6	0.055	40	After liberal diet with about 3.0 Kg. meat
7	6	0.075	65	After liberal diet with tbout 2.7 Kg. meat
8	6	0.022	35	After liberal diet with about 3.6 Kg. meat
9	5	0.002	20	After liberal diet with about 2.7 Kg. meat
10	6	0.023	50	After liberal diet with about 1.8 Kg. meat
11	3	0.006	50	After liberal diet with about 1.8 Kg. meat
12	5	0.026	80	After liberal diet with about 0.9 Kg. meat
13	5	0.040	60	After liberal diet with about 0.9 Kg. meat
14	4	0.010	10	After liberal diet with about 1.8 Kg. meat
15	5	0.112	40	After liberal diet with protein restriction
16	4	0.090	85	After 2 days of protein restriction
17	6	0.073	75	After 3 days of protein restriction
18	4	0.065	90	After 4 days of protein restriction
19	6	0.108	85	After 5 days of protein restriction
20	5	0.096	80	After 6 days of protein restriction
21	10	0.113	75	After modified fast day; about 100 calories
22	7	0.087	30	After liberal diet with 42 egg whites
23	9	0.094	55	After liberal diet with 36 egg whites
24	8	0.103	0	After liberal diet with 48 egg whites
25	6	0.135	85	After modified fast day; about 50 calories
26	6	0.060	0	After diet with 48 egg yolks
27	10	0.053	10	After diet with 48 egg yolks
28	8	0.065	100	After day of fasting
29	6	0.090	0	After 4,950 calories including 38 egg whites
30	7	0.103	15	After 2,500 calories including 29 egg whites
31	7	0.064	15	After 2,500 calories including 29 egg whites
Nov. 1	6	0.105	85	After day of fasting
2	8	0.089	35	After 2,700 calories including 6 eggs
3	7	0.080	85	After 2,400 calories with protein restriction

§ These gastric aspirations were made at thirty minute intervals early in the day (before eating or drinking).

* In calculating the percentage of bile contamination, a moderately strong bile tinge in each aspirate was regarded as 100 per cent contamination. Faint traces and unusual amounts of bile were allowed for accordingly.

† The earlier part of the period in this table is not strictly comparable to the latter part because of the difference in proximity to, and influence of, the prolonged fasting which ended September 13 and to which sixteen days of protein restriction were added.

the pylorus. Hence, in waiting for the tube to pass on one occasion, test aspirations were made whenever a sensation occurred. It was thus found that a sensation which was believed to be accompanied by the respiratory reflex developed twice as duodenal contents were regurgitated into the stomach. This observation suggested that the hunger sensation resulting from high acidity as well as that resulting from fat in the stomach might have been due to motility involved in the increased duodenal regurgitation which acid and fat are known to occasion. Moreover, the fact that regurgitation is increased during fasting (Boldy-

reff,[5] Carlson,[6] Hoelzel [4]), and the fact that it remained somewhat marked during the first four months after fasting, further supported the hypothesis that the hunger sensation with the respiratory increase was associated with regurgitation. In addition to this, a relation between protein starvation and increased regurgitation was suggested by data like those submitted in table 1. Here protein restriction was apparently a more direct cause of regurgitation than increased gastric acidity. Further observation, however, failed to substantiate consistently this otherwise interesting observation, perhaps because such violent contrasts in the protein intake did not occur again. Conclusive evidence also could not be obtained in support of the possibility that the hunger sensation with the change in the respiratory rate was associated only with duodenal regurgitation.

Summing up the evidence, it appears certain that the acid (and perhaps peptic activity) of the gastric secretion, by acting in the duodenum and mainly near the pylorus, was a factor in eliciting the hunger sensation with the respiratory increase. Whether the acid determined the sensation directly, or whether it gave rise to a pyloric or duodenal spasm or to some other form of motor activity which in turn elicited the sensation, is an unsettled question. The hunger sensation with the change in the respiratory rate was probably the hunger sensation which Boring found had occurred after the introduction of hydrochloric acid into the stomach. This sensation was probably also the "keen appetite" which, as Pawlow [7] observed, had developed after taking a little wine at a time when the desire to eat was not spontaneous. Moreover, the "appetite-like" sensation noted by Carlson after the administration of hydrochloric acid or of other fluids, which might have acted either directly or after stimulating the acid secretion, may have been a mild form of the hunger sensation with the increase in the respiratory rate—too mild to yield distinct objective evidence of such an increase. Besides this, the claim of Boldyreff [8] that the periodic gastric contractions do not give rise to hunger may be explainable by his further claim that the stomach is alkaline at such times; in contrast to this, American observers find more or less acid and hunger sensation. The lack of hunger in tuberculous subjects, in spite of essentially normal hunger contractions (Meyer [9]), may also be explainable by the low gastric acidity which is commonly found in patients with tuberculosis.

In this connection, it is interesting to note that Carlson found human gastric juice containing from 0.45 to 0.5 per cent hydrochloric acid effective in giving rise to sensation, but not that containing 0.2 per

5. Boldyreff, W.: Ergebn. d. Physiol. **11**:121, 1911.
6. Carlson, A. J.: Am. J. Physiol. **45**:120, 1918.
7. Pawlow, I. P.: The Work of the Digestive Glands, London, 1910.
8. Boldyreff, W.: Quart. J. Exper. Physiol. **10**:175, 1916.
9. Meyer, J.: Physiology of Stomach, Arch. Int. Med. **22**:759 (Dec.) 1918.

cent (Carlson and Braafladt[10]). Baird, Campbell and Hern[11] concluded that the duodenum is insensitive to twentieth normal or 0.2 per cent hydrochloric acid. Bársony and Egan,[12] using from 0.2 to 0.36 per cent hydrochloric acid and introducing from 3 to 15 cc. into the duodenum, observed that the smaller quantities and weaker acid had practically no effect, while the larger quantities and stronger acid nearly always gave rise to disagreeable sensations, nausea or dizziness, which, however, shortly disappeared. They also noted variations in the responses in different subjects. Wichert and Dworjetz[13] state that 10 cc. of tenth normal hydrochloric acid introduced into the duodenum gave rise to a disagreeable sensation or nausea unless the juice had been warmed. In tests made on two other subjects in our study, the repeated introduction of 25 cc. of 0.5 per cent hydrochloric acid into the stomach gave rise to a mild burning sensation which one of these subjects reported as involving an increased desire to eat. An increase in the respiratory rate, however, did not develop. It is common knowledge that hydrochloric acid frequently has a similar effect in cases of gastric achylia. Limiting ourselves to observations on man, these observations compare favorably with each other, as well as with the observations on F. H., particularly, if allowance is made for variations in the degree of sensibility.[14]

SOME OBSERVATIONS ON THE SENSIBILITY OF THE DIGESTIVE TRACT

It was pointed out in the preceding section that the hunger sensation with the increase in the respiratory rate was sometimes manifested when the acidity was relatively low after fasting as well as during fasting. Hence, if it is granted that ordinarily a relatively high gastric acidity is required to give rise to the sensation, some other factor must have favored the development of the sensation when the acidity was relatively low. This factor appears to have been increased sensibility. If it is not conceded that the gastric acidity played any rôle in eliciting the sensation, a consideration of the conditions again seems to compel us to assume increased sensibility to account for the sensation.

However, besides being a necessary assumption to explain the occurrence of the hunger sensation with the respiratory reflex, an increased sensibility of the digestive tract during fasting, protein starva-

10. Carlson, A. J., and Braafladt, L. H.: Am. J. Physiol. **36**:153, 1914.

11. Baird, M. McC.; Campbell, J. M. H., and Hern, J. R. B.: Guy's Hosp. Rep. **74**:23, 1924.

12. Bársony, T., and Egan, E.: München. med. Wchnschr. **72**:1242, 1925.

13. Wichert, M., and Dworjetz, W.: Arch. f. Verdaungskr. **34**:158, 1925.

14. Since this article was written the work of Palmer, which corroborates our observations in a number of ways, has been published. Palmer, W. L.: The Mechanism of Pain in Gastric and in Duodenal Ulcers, Arch. Int. Med. **38**:603 (Nov.) 1926; **38**:694 (Dec.) 1926; **39**:109 (Jan.) 1927.

tion and undernutrition was indicated by other observations. For instance, in connection with the study of the basal metabolism made by one of us (N. K.[1]), an attempt was made to insure uniform conditions in the digestive tract by having the subject (F. H.) ingest a quantity of nonnutritive bulky material shortly before determinations on the metabolism were made. Instead of guaranteeing gastric motor quiescence, however, as was to be expected from Carlson's [2] observations, periods of what appeared to be gastric hunger contractions were not inhibited, were prolonged or were actually initiated by the ingestion of this material (about 50 Gm. of cellulose flour soaked in petroleum jelly and taken with 50 cc. of water flavored with saccharin). The contractions (as recorded with the balloon method) sometimes appeared as early as three minutes after the ingestion of the mixture, which always gave rise to a sense of fulness. They usually continued until all the ingested material left, or was forced out of, the stomach—from one-half to one hour—and were generally felt as more or less gradually increasing hunger sensations. This was repeatedly observed during the period of about four months after the prolonged fasting, when the hunger sensation with the increase in the respiratory rate was manifested both with high and low gastric acidity. Later, however, the same quantity of nonnutritive material stopped the hunger contractions and occasionally remained in the stomach as long as three hours. This could only mean that the sensibility to mechanical stimuli had been increased on the previous occasions.

The experimentation necessary to yield similar objective data to show a hypersensibility to mechanical stimuli during prolonged fasting was not undertaken. However, because of subjective experience during previous fasts (Carlson,[6] Kunde [15]), F. H. restricted the use of nonnutritive bulk and even of water somewhat during the last two prolonged fasts (Hoelzel [4]). Bulk was used only during the latter part of the fasts and chiefly to promote forward peristalsis, as, after the third or fourth day of fasting, it was never possible to suppress the hunger sensations satisfactorily with nonnutritive material alone, regardless of how much was ingested. This does not mean that the ingestion of inert substances did not give rise to a sense of fulness; in fact, the sense of fulness usually developed quickly. This appeared to be due, at least in part, to an increase in gastric tonus which made it difficult to ingest large quantities, but which was also the prelude to a period of gastric contractions. Presumably, in certain pathologic states, similar motor responses of a hypersensitive stomach limit the amount of food which can be ingested with comfort, and may even give rise to painful sensation.

15. Kunde, M. M.: J. Metab. Research **3**:309, 1923.

Some observations also indicated that the mere presence of a balloon in the stomach, to record gastric motility, increased the motility somewhat during fasting and undernutrition. Comparison with subjective experience alone and with the data obtained by the aspiration method (Hoelzel [4]) pointed to this. Nevertheless, all methods of observation indicated a definite increase in motility during fasting and undernutrition. This raises the question whether the secretions in the hypersensitive digestive tract serve as the stimulus which gives rise to the increased motility. This would be practically certain if the accumulating secretions or excretions were an adequate, or normal stimulus of gastric motility as, for instance, Anitschkow [16] apparently would have us believe. But the work of Bulatao and Carlson [17] suggests that the blood sugar level is an important factor in determining gastric motility. Besides this, there is often gastric hypermotility in true achlorhydria. Without further data, we are therefore not in a position to decide whether the secretions should be accorded a material rôle.

The following instances may be cited as further evidence of an increased sensibility of the digestive tract resulting from fasting and undernutrition: 1. Carlson [18] found that smoking tended to produce nausea after a few days of fasting. He also refers to other evidence of a hypersensitive state. 2. Rütimeyer,[19] reporting the experience of a professional fasting woman, stated that she found it necessary to restrict the use of spices for some time after fasting. 3. The regrettable developments after the thirty-one day fast of Levanzin (Benedict [20]) were probably due to the use of food (lemons, etc.) which was irritating to a hypersensitive digestive tract. 4. On the twelfth day of a twenty-six day fast of F. H., nausea and burning sensations were occasioned as a result of swallowing a little gravel; such an effect was not noted when larger quantities of similar material were ingested under more normal circumstances. 5. F. H. found that he had made a mistake in breaking this twenty-six day fast with unsweetened (although highly diluted) lemonade. Excruciating burning and gnawing sensations developed and recurred periodically for twenty-four hours. Water gave no relief. Tomatoes aggravated the sensations. They disappeared after potatoes, fried with an excessive amount of fat, were eaten. 6. The only time that nausea was experienced during the thirty-three day fast of F. H. was after drinking some warm water on the thirty-second day; warm water did not have such an effect at other times. 7. Considerable violence was done when a salad of green pepper was used on the fifth day after the forty-one day fast of F. H. The subject had hardly ever eaten green

16. Anitschkow, S. W.: Ztschr. f. d. ges. exper. Med. **42**:405, 1924.
17. Bulatao, E., and Carlson, A. J.: Am. J. Physiol. **69**:107, 1924.
18. Carlson, A. J.: Am. J. Physiol. **33**:95, 1914. (Footnote 2.)
19. Rütimeyer, L.: Centralbl. f. innere Med. **30**:233, 1909.
20. Benedict, F. G.: A Study of Prolonged Fasting, Washington, 1915

pepper before, but it was tried at this time in a practically futile attempt to find something which would help to satisfy while the protein intake was being restricted for experimental purposes. The pepper, smothered in olive oil, was not observed to be particularly irritating to the taste, although it certainly was not bland. F. H. slept a few hours immediately after finishing the salad, and woke to find that his mouth and the rest of the digestive tract seemed to be "on fire." The burning sensation did not disappear entirely until about three days later, the blandest foods that suggested themselves being used in the meantime. This experience is hard to explain. Did it take several hours for a mild irritation of the mucous membrane of the mouth to become effective, by the gradual development of an inflammation; or did the pepper become effective mainly after absorption from the intestine, and give rise to a form of allergy? Whatever the explanation, this experience seemed to show decisively that there is a specific type of increased visceral sensibility. 8. In addition to the foregoing, candy and jam caused a burning sensation in the mouth, involving the tongue and gums, and in the throat when used to break a fast. This burning developed immediately on contact and usually disappeared within ten or fifteen minutes. It was not elicited again by the further ingestion of sweets. 9. Ice cream was always too cold to be relished for some time after fasting as well as during prolonged undernutrition. It was repeatedly felt to be so cold that its sweetness could not be tasted. Its coldness was felt practically all the way down the esophagus, this sensation disappearing at about the level of the cardia. 10. A specific type of sensibility was manifested during modified protein starvation thus: F. H. had frequently used celery in the normal diet without noting any unusual effect. After a few days of protein restriction, the juice of celery (taken to insure vitamin and salt balance) always gave rise to extreme dizziness or to a sinking sensation. This seemed to be a form of nausea without a feeling of disgust toward food. Other vegetable juices did not have such an effect. Celery alone or salted did not appeal to the taste during these periods, but it was particularly appreciated when mixed with other food. The effect, however, was always the same and independent of the manner in which it was taken. 11. The increased intestinal rate or improved bowel condition after fasting (Hoelzel,[21] Kunde [15]) is probably due to increased gastro-intestinal sensibility. 12. The exquisite taste of foods for some time after prolonged fasting may also only reflect increased sensibility.

These observations leave little room for doubt that the sensibility of the alimentary canal is increased as a consequence of fasting or undernutrition. That this hypersensibility is physiologic must be admitted,

21. Hoelzel, F.: The Rate of Progress of Food Residues Through the Bowel (privately published paper), 1924.

since realimentation always brings about more normal conditions. If it is granted that the increased sensibility is physiologic, what is its nature?

If conditions in the mouth and upper part of the esophagus are considered first, it will hardly be doubted that the increased sensibility is in the mucosa or other superficial structures. Such an explanation of increased sensibility in the lower part of the esophagus might, however, be questioned. Ryle,[22] for instance, leaves the impression that he regards heartburn as chiefly being due to contractions or spasms in the cardiac region. In support of this view, he cites Hurst's[23] observation that the esophagus is insensitive to hydrochloric acid. However, if the acid of the gastric contents gives rise to heartburn, it probably does so only after prolonged or repeated contact with the esophageal mucosa. Hurst's[23] report does not contain any evidence that he duplicated the probable conditions. These were closely simulated in the application of the method used by one of us (F. H.[4]) in securing data regarding the acidity and volume of the contents of the "empty" or fasting stomach. The aspirations were then made by first lowering the tube well into the stomach and then applying suction intermittently while the tube was gradually drawn back into the esophagus. The tube was always lowered a second time and occasionally a third time to repeat the process before an aspiration was considered complete, and the tube was withdrawn entirely. These aspirations were usually made at intervals of half an hour and were sometimes repeated from ten to thirty-two times in one day. It was originally intended to avoid swallowing saliva throughout the periods of observation, but it soon became evident that this was impracticable. The reason was that the acid adhering to the tube and being repeatedly brought into the esophagus gave rise to a burning sensation, apparently heartburn. Consequently the swallowing of saliva was generally completely avoided only during actual intubation. A burning sensation developed most rapidly when the gastric acidity was relatively high, but heartburn was also distinctly experienced (during digestion) when the acidity was relatively low; at that time, gastric regurgitation occurred frequently. This evidently occasioned a more or less continuous irritation of the esophagus by the gastric contents and led to heartburn in spite of the relatively low acidity. The gastric regurgitation probably occasioned concomitant variations in pressure or contractions in the esophagus, such as Payne and Poulton[24] found associated with heartburn. There is no evidence, however, that such contractions alone could give rise to a burning sensation.

22. Ryle, J. A.: Gastric Function in Health and Disease, London, 1926.
23. Hurst, A. F.: The Sensibility of the Alimentary Canal, London, 1911.
24. Payne, W. W., and Poulton, E. P.: Quart. J. Med. **17**:53, 1923.

This, however, does not mean that the sensation in heartburn comes from the mucosa. If the intact esophageal mucosa gave rise to sensation, the sensory response to acid might well be expected to be immediate. But as the burning sensations in the experience of F. H. developed gradually, and as (slight) bleeding at the cardia was eventually and repeatedly occasioned when aspirations were continued after pain began (Hoelzel [1]), the sensation evidently came from the submucosal structures, possibly as a result of the irritation of afferent fibers accompanying the blood vessels. Breslauer,[25] Kappis,[26] Propping [27] and Ritter,[28] among others who studied visceral sensibility, concluded that sensory nerves accompany the larger blood vessels. However, the work of Odermatt [29] indicates that sensory nerves also accompany or surround the capillaries, and that they respond chiefly to chemical stimuli, especially, when such stimuli are applied under pressure. Odermatt's observations therefore make it seem possible that adequate chemical stimuli, particularly when assisted by pressure caused by increased tonus or contractions, may elicit sensation anywhere in the digestive tract provided the mucosa is penetrated.

Besides suggesting the nature of the sensibility involved in heartburn, the experience of F. H., principally when bleeding was produced at the cardia, emphasized the difficulty of localizing the exact site of some types of visceral sensation by subjective analysis alone. It was clear at first that some burning came from the esophagus as the sensation was rather high. However, by swallowing a little saliva after each aspiration, irritation by acid at a high level was prevented. When the gastric acidity was greater than usual, it was impossible to prevent the development of pain at lower levels; the stomach then appeared to become raw when the aspiration periods were prolonged. It was some time before it was noticed that the pain was always particularly sharp (sometimes like a toothache) when suction was applied while the tip of the tube was at the level of the cardia. It is not likely that there was any specially sensitive spot lower down in the stomach, and yet the entire stomach appeared to be raw. In view of this, it is easy to understand that similar sensation elicited at other circumscribed sites, either in or somewhat beyond the stomach, may also be sufficiently diffuse to be referred to the gastric region in a general way. Nevertheless, as Ryle's [30] and our own observations indicate, sensations which are apparently caused by contractions alone are usually more definitely localized.

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25. Breslauer, F.: Beitr. z. klin. Chir. **121**:301, 1921.
26. Kappis, M.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **26**:493, 1913.
27. Propping: Beitr. z. klin. Chir. **63**:690, 1909.
28. Ritter, C.: Zentralbl. f. Chir. **35**:609, 1908; Arch. f. klin. Chir. **90**:389, 1909.
29. Odermatt, W.: Beitr. z. klin. Chir. **127**:1, 1922.
30. Ryle, J. A.: Lancet **1**:895, 1926.

If we next consider gastric sensibility on the assumption that sensation due to chemical stimuli comes mainly by way of afferent fibers in the submucosa or by way of perivascular nerves, it follows that such stimuli cannot reach these fibers easily, since the normal gastric (fundal) mucosa is practically impermeable to most substances. Alcohol is an exception and likewise is said to give rise to sensation from the stomach (Carlson,[2] Hurst [23]). However, with an injured, inflamed or ulcerated mucosa, conditions would be altered. Claims, like that of Hurst, that even the ulcerated gastric mucosa is insensitive to hydrochloric acid can be met by counter-claims. Thus, Palmer, working at the Cook County Hospital, found the sensibility to hydrochloric acid sufficiently uniform to use it (hydrochloric acid introduced into the stomach) as a test for the presence, or proof of the cure, of an ulcer (personal communication [14]). Sensation from an injured gastric mucosa was probably involved on one occasion when increasingly painful and practically continuous burning and gnawing sensations were experienced by F. H. after the ingestion of seventeen lemons. As the eating of the lemons made the tongue and gums bleed (thus making it too painful to ingest more), the gastric mucosa was probably also affected. The painful gnawing was evidently partly due to the digestive contractions. The eating of fat brought relief.

The opinion was previously held by one of us (F. H.) that the normal gastric mucosa possessed a degree of tactile sensibility. This view seemed necessary to explain an element in hunger sensation which did not appear to be referable to contractions of the muscularis alone. Accordingly, some tests were made during one period by swallowing a quantity of barely moistened knotted string or millet seed after first removing the gastric residuum. These substances were swallowed thus because it was not possible to force them through an aspiration tube in the dry state. However, instead of the expected hunger or hunger-like sensations (which arose in a few preliminary tests when the gastric residuum was not first removed), thirst developed. This thirst again disappeared within about thirty minutes without drinking. It apparently lasted until sufficient gastric juice was secreted to soak thoroughly the barely moist material which had been swallowed. This perhaps means that there is a gastric (or duodenal) component in thirst. The sensation involved here seemed to be a vague or dull burning referable to the epigastric region rather than a sense of dryness referable to the pharynx. An intestinal component in thirst was believed previously to be indicated by the observation that thirst, which would again disappear without drinking, often developed with diarrhea. Gastrointestinal conditions may also explain the thirst or sense of dryness which cannot be relieved by drinking, and which was observed during fasting by Kunde [15] and in some fasts by F. H.

The problem of gastric sensibility is complicated by the fact that most test substances introduced into the stomach pass into the duodenum and may give rise to sensation there. Without check tests on the duodenum, it is not certain that a sensation has actually come from the stomach. Granting, however, that it comes from the stomach, this does not tell us whether the sensation comes from the stomach as a whole or only from a circumscribed site. London,[31] for instance, presents evidence that the sensation of fulness comes from the cardia. The observations of Rogers and Martin [32] suggest that the gastric contractions may give rise to hunger sensation from a position near the pylorus. In fact, it seems probable that the hunger sensation comes from this region rather than from the fundus, because the contractions close to the pylorus are stronger than those in the fundus (Moritz [33]), and because the functional rôle of the antrum in gastric physiology is such that it appears to be a more probable site of sensibility than the fundus.

Chemical stimuli would be more likely to cause sensation in the duodenum (and in the gastric antrum) than in the fundus of the stomach, for the increased power of absorption here is evidence of a more permeable mucosa. This does not exclude the possibility or the practical certainty that contractions of the duodenum are also involved in, or may independently give rise to, sensation—apparently, with antiperistalsis, contributing to the sensation of nausea (Alvarez,[34] Fitzgibbon,[35] Ivy and Vloedman,[36] Keeton [37] and Wheelon [38]). But as motility usually involves a shifting of the contents of the digestive tract, peristaltic activity may bring acid gastric contents into the duodenum, and, as evidence presented in the preceding section indicates, under some conditions, the acid may give rise to a more intense hunger sensation than some gastric hunger contractions. On the other hand, nausea, headache, dizziness, some weakness and so-called symptoms of autointoxication are probably often the result of the irritation of the sensitive duodenum by contents which have been brought from a lower level of the digestive tract, or which remain stagnating in the duodenum.

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31. London, E. S.: Experimentelle Physiologie und Pathologie der Verdauung, Berlin, 1925.

32. Rogers, F. T., and Martin, C. L.: Am. J. Physiol. **76**:349, 1926.

33. Moritz, F.: Ztschr. f. Biol. **32**:313, 1895.

34. Alvarez, W. C.: Reverse Peristalsis in the Bowel, A Precursor of Vomiting, J. A. M. A. **85**:1051 (Oct. 3) 1925.

35. Fitzgibbon, J. H.: Reverse Peristalsis Associated with Nausea, J. A. M. A. **85**:1889 (Dec. 12) 1925.

36. Ivy, A. C., and Vloedman, D. A.: Am. J. Physiol. **72**:99, 1925.

37. Keeton, R. W.: Nausea and Related Sensations Elicited by Duodenal Stimulation, Arch. Int. Med. **35**:687 (June) 1925.

38. Wheelon, H.: Symptoms Associated with Duodenal Retention and Reverse Motility, J. A. M. A. **86**:326 (Jan. 30) 1926.

However, whether hunger sensation and nausea are more directly referable to motor activity or to chemical stimulation, it is significant that the duodenum apparently contributes to both sensations. Nausea is often thought of as the direct antithesis of hunger; but both are related to food intake—hunger being a craving for, and nausea a feeling against, the ingestion of food, while a conception of satiety as the neutral point between hunger and nausea might be defended. The fact that some people are nauseated when hungry, or that they cannot distinguish clearly between the sensations (Boring [3]) indicates an element of similarity. One of us (N. K.) has personally experienced this confusion from time to time, while F. H. has often found that symptoms of autointoxication (dopiness, weakness and mild headache) either cleared up or decreased considerably with periods of hunger contractions which normally involved a predominance of powerful forward peristalsis. The simultaneous manifestation of nausea, satiety and hunger (or appetite) also seems easily demonstrable. For instance, whenever F. H. attempted to satisfy hunger with a diet restricted to fat, the feeling that enough had been ingested (satiety regarding fat) soon developed. A keen desire to eat (other food) might persist, but nausea would develop when attempts were made to satisfy this desire by the ingestion of more fat. Proteins or carbohydrates would be eaten with avidity on such occasions. An excessive fat intake evidently provokes nausea by increasing antiperistalsis, as suggested by the duodenal regurgitation which fat is known to excite. The blending of nausea and the hunger sensation makes it appear that there is an overlapping of the sites of origin of the two sensations, or that both come from the same site but are elicited by different stimuli. This site seems to be the parapyloric region (gastric antrum, pylorus and first part of the duodenum). Whether the sensations are caused by motility, by chemical stimuli or by both, the variety of motor and chemical activity in this region could account for every kind and degree of sensation related to food—including idiosyncrasies and the unusual cravings often associated with pregnancy (the cause of which is suggested by hyperemesis gravidarum).

After what has been said, little need be added concerning the probable immediate cause of the increased sensibility of the digestive tract induced by fasting and undernutrition. The development of edema as a result of protein deficiency (Kohman [39]) after fasting (Hoelzel,[14] Kunde [40]) or with malnutrition (Jackson,[41] Morgulis [42]) shows that a more or less generalized increased permeability is involved in each case.

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39. Kohman, E.: Am. J. Physiol. **51**:378, 1920.

40. Kunde, M. M.: Edema, Arch. Int. Med. **38**:57 (July 15) 1926.

41. Jackson, C. M.: The Effects of Inanition and Malnutrition upon Growth and Structure, Philadelphia, 1925.

42. Morgulis, S.: Fasting and Undernutrition, New York, 1923.

This would account for the increased sensibility to chemical stimuli in the digestive tract and incidentally might explain the increased gastric acidity (after fasting or protein starvation) which, in turn, appears to be a powerful stimulus of sensation.

THE PROBLEM OF SPECIFIC HUNGER SENSATION

Evvard [43] found that hogs were able to select their food instinctively better than nutrition experts could choose it for them. Mitchell and Mendel [44] observed that rats and mice could, to a large extent, discriminate between adequate and inadequate diets. Rubner [45] pointed out that various races of mankind instinctively use diets with a total calory intake well adjusted to needs and with a protein ratio which is strikingly uniform, although the sources of the food elements vary widely. This seems to indicate that normally some fundamental physiologic factors impel animals and man to take fairly adequate quantities of the various food elements. That is, the foregoing observations suggest that the general urge to eat is a complex—the sum of a number of simpler urges or specific hunger drives. Such a view of hunger at least appears worthy of consideration.

Thirst is apparently a type of specific hunger. The young mammal or the human infant, normally receiving milk to satisfy both hunger and thirst, can hardly be aware of thirst as distinct from hunger. The probability is that it is usually a little thirsty when it is hungry, and generally a little hungry whenever it is thirsty. All that such a young animal can become aware of is that it wants to suckle, or that it wants "more"—more milk. Maturer animals, including man, would hardly become more aware of a distinct sense of thirst than a fish if the diet always contained enough or more than enough water. In support of such a view, it is of interest to find a psychologist like McDougall [46] saying that mild sensations of hunger and thirst seem alike. To distinguish, he takes a drink of water. If that satisfies, he was thirsty; if not, he was hungry! F. H. has met with similar confusion. During some periods he used large quantities of fresh fruit in a salt-free diet. The diet, consequently, contained more than enough water to prevent thirst under ordinary conditions. Sometimes three or four months would pass without an occasion arising which would call for a drink. When hot weather set in after such a period, additional water was occasionally called for, but thirst was not recognized immediately. What was noticed then was a sense of discomfort or a hunger-like sensation involving a desire for "something," but accompanied by the

43. Evvard, J. M.: Proc. Iowa Acad. Sc. **22**:375, 1915.
44. Mitchell, H. S., and Mendel, L. B.: Am. J. Physiol. **58**:211, 1921.
45. Rubner, M.: Deutsche med. Wchnschr. **51**:259, 1925.
46. McDougall, W.: Outline of Psychology, New York, 1923.

feeling that food would not be relished. Some might call it hunger without appetite (for the usual food). Generally, the fact that thirst was being experienced dawned on the mind when the subject came in contact with water (as in washing the hands). After the distinction between hunger and thirst was thus revived, it became easy to discriminate again later. A gastro-intestinal factor in thirst, such as has already been referred to, might be the source of possible confusion, or serve as a link, between thirst sensation and hunger in general. At any rate, these considerations seem to make it logical to regard thirst as a specific type of hunger—water hunger—as Durig [47] considers it.

As the foregoing indicates, we apparently come to distinguish between thirst and ordinary hunger (the desire for the other food elements) mainly because sharp contrasts are often brought about, and because a specific element (water) free from gross admixture with other elements exists and is frequently used to satisfy this particular craving independently. This points to the way in which we can determine experimentally whether ordinary hunger is not a complex made up of simpler urges, such as, protein hunger, carbohydrate hunger, salt hunger and vitamin or other types of hunger. It was with this conception in mind that an experimental search for evidence of a protein hunger sensation (because of the vital importance of protein) was begun by one of us (Hoelzel [4]). The assumption was that if a protein hunger sensation exists, observations made while the protein intake was sufficiently varied should give evidence of such a sensation. The first observation was that the gastric acidity is raised by protein restriction and is again lowered by protein realimentation (Hoelzel [4]). This observation was partly accidental, as it was more or less incidental to an investigation of the relation of gastric acidity to hunger in general (Hoelzel [4]). It was also observed that, as a consequence of modified protein starvation, peculiarly persistent hunger sensations developed which could be dispelled only by protein realimentation. As indicated in a preceding section, it then became clear that this hunger involved the sensation which strikingly increased the respiratory rate. Therefore, the conclusion seems warranted that the hunger sensation with the increase in the respiratory rate is an index of protein hunger, just as pharyngeal dryness (Cannon [48]) or esophageal contractions (Müller [49]) and a possible gastric or intestinal factor (F. H.) indicate thirst. To say that the sensation with the respiratory reflex is an index of protein appetite, instead of protein hunger, would be to ignore important facts and fundamentals. In the first place, the sensation gives no direct indication that protein is desired. That is discovered by trial and error.

47. Durig, A.: Appetit, Vienna, 1925.
48. Cannon, W. B.: Proc. Roy. Soc. Lond. Ser. B, **90**:283, 1918.
49. Müller, L. R.: Deutsche med. Wchnschr. **46**:113, 1920.

Moreover, prolonged protein restriction appears to decrease protein appetite; that is, it tends to make one forget the taste of protein food just as prolonged fasting may make one indifferent to customary foods. Besides this, a sensation which is strong enough to "take the breath away" is as logically referred to as hunger as the ordinary hunger sensation which has little, if any, effect on respiration.

The question may well be raised here whether the ordinary hunger sensation, which is more or less directly associated with the gastric motor activity, is in any sense an index of a specific need. A number of observations make it highly probable that the ordinary hunger sensation most directly reflects the carbohydrate need. In support of this there is, in the first place, the observation of Bulatao and Carlson [17] that the hunger contractions can be influenced strikingly by the blood sugar level. About the same time, Harris [50] reported the observation of hypoglycemia in patients who became hungry or weak soon after a meal. Luckhardt's [51] earlier observation of abnormally strong hunger contractions in diabetes also pointed to a relation between carbohydrate metabolism and the gastric contractions. Obviously, it is not the blood sugar level but the utilizable sugar that counts. The common experience that sweets before a meal may quickly dissipate hunger is perhaps to be explained mainly by the effect of the carbohydrate on gastrointestinal motility or tonus. An earlier practice of F. H. in beginning a fast might also be mentioned here. This was to eat nothing but sweets on the day before fasting. It was then possible to abstain from food with ease for at least one day. An excess in the use of sweets evidently also accounts for the frequent lack of "appetite" after parties or holidays.

In view of considerations like the foregoing, some observations were made with the balloon method of study to determine the specific effect of variations in the carbohydrate intake while the protein intake was adequate and fairly constant. It was thus found that, while a period of gastric hunger contractions did not develop during as long a time as six hours following the emptying of the stomach after a high carbohydrate intake, with complete carbohydrate restriction, periodic motor activity was manifested even during digestion, that is, after the ingestion of a meal of fat (fig. 4). However, it was not possible to lengthen progressively the time between the periodic gastric contractions by a prolonged high carbohydrate intake. In fact, the periods again became more frequent under such circumstances. On the other hand, with a continued high fat intake, the intervals between the periods became longer after an initial shortening. The explanation may be that a

50. Harris, S.: Hyperinsulinism and Dysinsulinism, J. A. M. A. **83**:729 (Sept. 6) 1924.

51. Luckhardt, A. B.: Am. J. Physiol. **33**:313, 1914.

Fig. 4.—Periodic element in gastric motor activity during digestion of meal of fat (115 Gm. butter); time in minutes given below.

habitual high carbohydrate intake leads to a quicker response in the glycogenic function, as suggested by Bock and others.[52] This would tend to nullify the effect of the carbohydrate excess which would otherwise depress motility. A continued high fat intake leads to a rise in blood sugar (Weeks and others[53]) which perhaps counteracts the initial effect of this type of dietary excess and again lengthens the intervals between the periodic contractions. In other words, an adaptation to the use of excessive quantities of fat or carbohydrate may take place. The effects of variations in the carbohydrate and fat intakes are therefore obscured in prolonged experiments, but seem clear in briefer tests.

The aforementioned observation of periodic motility during the digestion of meals of fat is of particular interest. It seems possible to explain this occurrence as follows: Periodic motility is probably an autonomic function of the digestive tract. This, however, can be modified considerably by variation in the blood sugar level or utilizable carbohydrate. By the ingestion of meals containing carbohydrate (or protein which serves as source of carbohydrate), the periodic element in motility may be suppressed by the absorbed carbohydrate, which cannot occur when the meals contain an excess of fat or fat only. Nevertheless, variations in glycogenesis or in pancreatic (insulin) secretion also appear likely to modify the results. This deduction is made from the observations of Harris as well as from our own observation of a period of increased motility which developed on one occasion during the digestion of a carbohydrate meal and once after the ingestion of a protein meal, before the stomach had been emptied. This periodic motility was usually experienced as mild hunger. In fact, the subjective experience of hunger shortly after the ingestion of meals of fat led to the investigation. That this periodic digestive motility is not a peculiarity of the subject (F. H.) is shown by the independent finding, by Mulinos,[54] of a similar phenomenon in dogs. Carman[55] also stated that, contrary to the teaching of Cannon[56] and others, he sometimes observed (with the roentgen ray) that a period of gastric motor activity at the beginning of digestion was followed by a brief period of relative or complete inactivity. Some irregularities in digestive motility should therefore be regarded as normal. Naturally, it is more difficult to discover such fluctuations in motor activity with the limitations of the

52. Bock, J. C.; Schneider, H., and Gilbert, M.: J. Biol. Chem. **69**:9, 1926.

53. Weeks, D. F.; Renner, D. S.; Allen, F. M., and Wishart, M. B.: J. Metab. Research **3**:317, 1923.

54. Mulinos, M. G.: Am. J. Physiol. **77**:158, 1926.

55. Carman, R. D.: The Roentgen Diagnosis of Diseases of the Alimentary Canal, Philadelphia, 1921.

56. Cannon, W. B.: The Mechanical Factors of Digestion, New York, 1911.

roentgen-ray method of study than with the more continuous record obtainable by the balloon method.

The changes in the gastric hunger contractions observed during prolonged fasting also seem to be largely explainable by the alteration in the carbohydrate metabolism as reflected by variations in the blood sugar level. The determinations for blood sugar, as shown in table 2, were made during the thirty-three day fast of F. H., by Dr. Larson of the University of Illinois College of Medicine by courtesy of Prof. Welker's arrangement.

These figures show that the blood sugar decreased at the beginning of fasting and remained at a low level throughout. It did not decrease continuously. Likewise, gastric motility increased over the prefasting motility, but it apparently did not continue to increase after the first few days (fig. 5). Irregular variations in the frequency and intensity of the hunger periods were noted; likewise, the blood sugar level varied. A

TABLE 2.—*The Determinations for Blood Sugar During the Thirty-Three Day Fast*

Date (1925)		Per Cent
May 28	First day of fast	0.087
June 1	Fifth day of fast	0.058
5	Ninth day of fast	0.043
9	Thirteenth day of fast	0.067
16	Twentieth day of fast	0.069
22	Twenty-fourth day of fast	0.058
July 1	Four hours after breaking fast*	0.094
7	Before eating; six days after fast	0.104

* The carbon dioxide combining power of the blood (determined by Dr. Kunde) was 39 before, and 52 four hours after, breaking the fast.

closer relationship could not be claimed without more data. The variations suggest that considerable changes may occur within a few hours. There is also a suggestion that the blood sugar level paralleled the curve of gastric acidity (Hoelzel [4]) in increasing after an initial decrease. Lennox [57] recently reported the observation of similar variations in the blood sugar level during fasting.

The foregoing observations make it highly probable that the gastric hunger contractions more or less directly reflect the carbohydrate need. However, in view of the relation of the carbohydrate reserve in man to the nutritive state in general, carbohydrate hunger probably also indicates the total caloric need. Ordinary hunger, as Harris has suggested, may therefore primarily be a desire for glucose. Hence, the gastric hunger contractions apparently serve simultaneously to give rise to a specific and also to a nonspecific hunger sensation. The nonspecific element is obviously emphasized, because the general desire to eat is somewhat intimately related to the degree of emptiness of the stomach.

57. Lennox, W. G.; O'Connor, M., and Bellinger, M.: Chemical Changes in the Blood During Fasting in the Human Subject, Arch. Int. Med. **38**:553 (Nov.) 1926.

Besides thirst, protein hunger and carbohydrate hunger, there are a number of manifestations of specific hunger which future investigation may prove to involve characteristic peripheral sensation complexes, although they may also be of central origin. Among these is the well known salt hunger of some herbivores. The seeming lure of the water of certain springs for some invalids, especially when benefit is obtained, probably also indicates a specific salt hunger. The osteophagia of cattle is a well investigated type of specific hunger. To refer to it as a perverted appetite (Green [58]), when it reflects a physiologic need for phosphorus, is obviously illogical. It would seem more consistent to say that cattle that do not eat bones, when they are available, and when phosphorus is deficient in the natural food supply, have a perverted appetite (more correctly, perhaps, a perverted hunger). Durig [47] refers to the fat hunger experienced in the central empires during the war, and may be

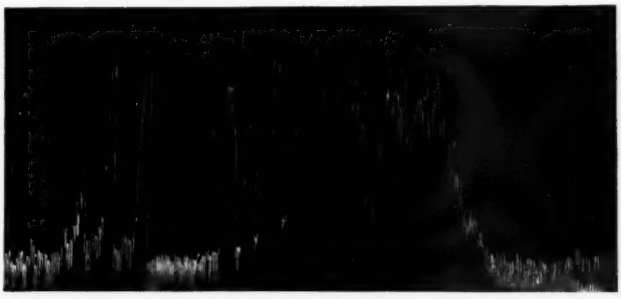

Fig. 5.—Period of gastric hunger contractions of F. H. on fortieth day of fasting; total time, twenty minutes.

right in suggesting that this probably involved a call for vitamins. Vitamin hunger seems to be the explanation of the following experience. Before F. H. had any knowledge of vitamin A, it was observed that, after using only olive oil as food for a few days, butter mixed with sugar tasted better than anything else, with the possible exception of ice cream. Why the ingestion of one fat food (olive oil) should lead to a particular liking for another fat food (butter or cream) was not explainable until a few years later when the fat-soluble vitamin A became known. The exclusive use of olive oil apparently created a vitamin A hunger. The particular craving for sugar in this experience is understandable when the rôle of carbohydrate in ordinary fat metabolism is borne in mind. In this connection, it seems significant that it has not been possible to find a specific sensation complex which might be an index of a need of fat. Perhaps fat and carbohydrate, being more or less

58. Green, H. H.: Physiol. Rev. **5**:336, 1925.

physiologic substitutes for one another, are craved in much the same way —by sensation mainly referable to gastric motility.

However, aside from the evidence of specific hunger which has been given, the observations in vitamin deficiency studies suggest that specific hunger sensation is an inevitable consequence of specific starvation. As is well known now, the deficiency of essential food elements usually gives rise to characteristic symptom complexes in which the digestive tract is generally involved (McCarrison,[59] Cowgill and others[60]). When not carried to pathologic extremes, the symptoms can be remedied by supplying the proper food. The repeated alleviation of specific symptoms, whatever their nature or however mild, by the ingestion of particular food elements would naturally lead to such symptoms being regarded as the index of hunger for the corresponding elements. Such a relationship and association between the unpleasant gastric sensations and the food intake in general Carlson[12] believed explained the reference of hunger to the stomach; nothing further has been proved to explain the relation of thirst to specific sensations which are said to indicate it.

According to the foregoing, hunger viewed as a special instinct would normally serve as a guide in nutrition, but it is commonly believed that often this is not true. Without more precise experimental data, we can here only suggest the factors which may account for the apparent exceptions. First, a normal manifestation of hunger demands the normal functioning of the physiologic mechanism involved. Abnormalities may occur in this mechanism just as they occur elsewhere. Second, granting a normal hunger mechanism, the development of a normal (conscious) use of this mechanism (appetite) obviously depends on the use of adequate food while the psychic relationships between hunger and food intake (taste-memory processes) are becoming more or less fixed. It is also perhaps not always borne in mind that hunger does not tell us what to eat; it serves primarily to impel us to try things. Whether man will even try those foods which would yield the most fundamental or most complete degree of satisfaction depends largely on environmental, cultural and educational factors. Third, there is a quantitative factor in hunger whereby the elements of which the largest amounts are needed (carbohydrate, fat and protein) become most prominent. The habitual relative overuse of such elements may therefore tend to develop naturally. Fourth, with a surplus of food, such as commonly obtains among mankind, the tendency is to reject food which is less agreeable with respect to texture and taste. Hence, greenstuffs which are often not only coarse textured, but which may con-

59. McCarrison, R.: Studies in Deficiency Diseases, London, 1921.

60. Cowgill, G. R.; Deuel, H. J., Jr.; Plummer, N., and Messer, F. C.: Am. J. Physiol. **77**:389, 1926.

tain distasteful or even toxic ingredients (tannin, etc.) will naturally be used sparingly, especially when a fair degree of satisfaction is yielded by the liberal use of slightly deficient but otherwise more agreeable food. If, however, a sufficiently acute hunger for essential food elements is created by prolonged fasting or specific starvation, foods (such as greens) which may otherwise be regarded as disagreeable are likely to be relished far more than foods (such as sweets) which are ordinarily preferred. This has been a common experience of F. H. Taste or appetite therefore may not be a safe guide in nutrition, but appetite is not hunger ("instinct").

COMMENT

Much of the foregoing is based on observations made on only one subject. Obviously, similar studies on other subjects would be desirable and would have been made if the necessary subjects had been available. In fact, some of the experimentation with F. H. was not carried further because it was felt that the fundamental observations should be confirmed on others. The protein hunger sensation was not observed during the fifteen day fast of F. H. studied by Carlson,[6] but evidence of it may have escaped notice. The published records of gastric motility during that fast are not clear enough to give definite evidence, and the unpublished graphs were unfortunately destroyed after having been saved for four years. A consideration of all the factors involved also gives the impression that the sensation may develop sooner with simple but rigid protein restriction than with complete fasting. Aside from this, the possibility that others may be affected differently from F. H. cannot be entirely disregarded; on the other hand, it does not seem likely that anything so fundamental would vary much in different persons. In this connection, it should perhaps also be emphasized that the protein hunger sensation continued to be manifested for four months after fasting only because of the experimental dieting of that period. With a continued adequate protein intake immediately after the forty-one day fast, the sensation probably would have disappeared within three weeks.

A weak point in our study is involved in the fact that respiration can be affected by conscious attention with relative ease. Reasons were given which indicate that our results cannot be thus explained away. Nevertheless, it has since been thought that it might have been better to observe the heart rate, assuming that it is affected by the protein hunger sensation. Electrocardiograms during such hunger might also reveal something of interest. One taken during digestion, a few days after the thirty-three day fast, showed nothing in spite of marked edema (Kunde [40]). The heart, however, is probably affected in some way by prolonged restriction of protein. Transient sensations, as if one would collapse unless proper food were taken, were noted from time to

time by F. H., and were thought to be due to circulatory disturbances. The suspicion arises that it was some such sensation, rather than alarm over a low excretion of nitrogen, which terminated the rigid protein restriction experiment reported by Smith.[61] A subject who knew nothing about the excretion of nitrogen would probably have felt as much "alarmed" and might have stopped just as soon or sooner.

SUMMARY

Evidence of a specific type of hunger sensation, which gave rise to a striking increase in the respiratory rate, has been obtained (in one subject). This sensation was somewhat independent of the periodic gastric hunger contractions. Under extreme conditions, it was manifested even with food in the stomach. It differed from the ordinary hunger sensation mainly in being more diffuse or more radiating.

This peculiar hunger sensation appeared to be elicited chiefly by the action of the gastric contents in a hypersensitive duodenum. Increased sensibility, however, was a more important factor than gastric acidity. Evidence is given which indicates that fasting, protein starvation or undernutrition may give rise to a hypersensitive state in the digestive tract.

As the hunger sensation with the increase in the respiratory rate developed repeatedly in consequence of protein starvation (including fasting in this category), and as it could easily be suppressed by protein realimentation, this sensation is believed to be an index of protein hunger. The gastric hunger contractions and tonus variations are shown to reflect the carbohydrate need to a large extent. A gastro-intestinal component in thirst, which would tend to link thirst with hunger sensation, was also believed to be found.

These observations and other considerations are thought to support the view that the general complex of hunger sensation is comprised of a number of simpler specific urges or conditions which normally impel a fairly adequate intake of the various food elements. However, in contrast to hunger, taste or appetite may not be safe guides in nutrition.

61. Smith, M.: J. Biol. Chem. **68**:15, 1926.

SEVERE CHRONIC GLOMERULAR NEPHRITIS

WITHOUT HYPERTENSION, CARDIAC HYPERTROPHY OR RETINAL CHANGES: REPORT OF TWO CASES *

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ROCHESTER, MINN.

For many years medical teaching has emphasized the association of hypertension, cardiac hypertrophy and retinal changes in the severe cases of chronic glomerular nephritis. These observations have been so reliable in most cases, especially in those with marked retention of nitrogen, that physicians have learned to rely on them as valuable aids in differential diagnosis, and to regard one or more of these three observations as almost necessary for a correct diagnosis of chronic glomerular nephritis with uremia. Rare exceptions to this general rule, however, have long been recognized. In 1905, Müller [1] mentioned the association of tuberculosis, acute sepsis, typhoid fever and ascending renal infections with some cases of chronic diffuse nephritis in which elevation of blood pressure or cardiac hypertrophy did not occur. In certain of these cases the greater part of the kidney was destroyed, but true uremia was rare.

In 1908, Jores [2] showed that the degree of destruction of tissue in the kidney could not be the decisive, causative factor of cardiac hypertrophy or elevation of blood pressure. He found typical examples of granular atrophy of the kidneys in which both the arterial tension and the size of the heart were normal.

In 1922, Foster [3] described two cases in which nephritis had developed in early life and in which death had occurred before the twentieth year. The blood pressure had been normal throughout the disease. At necropsy the kidneys were smaller than normal and granular. Sections showed the ordinary picture of chronic glomerular nephritis. More recently, French writers [4] have reported "chronic nephritis with azotemia and without arterial hypertension," but although their cases were some-

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* From The Mayo Foundation.

1. Müller, Friedrich: Morobus Brightii, Verhandl. d. deutsch. Gesellsch. f. Chir. **7-9**:64, 1905.

2. Jores, Leonard: Ueber die Beziehungen der Schrumpfnieren zur Herzhypertrophie von pathologische-anatomischen Standpunkt, Deutsches Arch. f. klin. Med. **94**:1, 1908.

3. Foster, N. B.: The Relations of Hypertension to Cardiorenal Diseases, Am. J. M. Sc. **164**:808, 1922.

4. Bouchut, L., and Ravault, P.: Les néphritis chroniques azotémiques, Presse méd. **1**:67, 1926. Laroche, Guy, and Desmoulière, A.: Les néphritis chroniques urémigenès, Presse méd. **2**:689, 1924.

what similar to, they did not seem to coincide entirely with, the group under discussion.

Although these unusual cases have been recognized and some of them reported, there is great need of more clinical data in order to study and appreciate better the relationship of hypertension and cardiac hypertrophy to nephritis, a point emphasized by Foster and others. It is for this purpose that the following cases are reported.

In case 1 the records are complete and permit conclusions to be drawn which are definite enough to give title to this article. In the second case the data are not so complete, and all of the blood pressure readings not so definitely normal as in case 1, but the two cases are similar and so unusual that it seems advisable to report both.

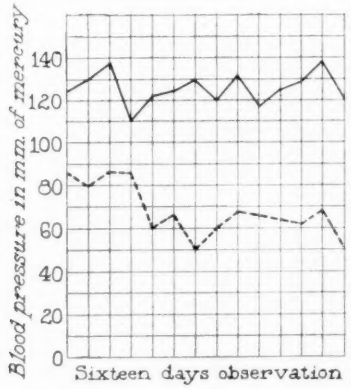

Fig. 1.—Blood pressure readings in case 1. Note that systolic pressures higher than 140 and diastolic pressures higher than 90 were not observed. The continuous line indicates systolic pressure, the broken line, diastolic pressure.

Case 1.—A man, aged 49, was admitted to the Clinic on Feb. 25, 1926, complaining of weakness and vomiting. He had been a gold miner for the past seven years. Following influenza in 1919, he had noticed a slightly productive cough and some loss of weight for several months, but he had gradually recovered. About Dec. 1, 1925, he contracted a cold. This was followed by malaise, slight anorexia and some loss of weight and strength. However, he continued to work until early in February, when he became profoundly weak and began to vomit soon after eating. Because of the persistent vomiting and loss in weight of more than 20 pounds (9 Kg.) cancer was suspected, and he was referred to the Clinic.

The patient showed clinical evidence of uremia with associated weakness, dehydration and moderate anemia and was admitted to the hospital immediately. Although the blood contained 304 mg. of urea and 15.6 mg. of creatinine for each 100 cc., the blood pressure was only 124 systolic and 86 diastolic. The eyegrounds appeared normal except for slight anemia; there were no signs of cardiac hypertrophy or decompensation, and there was little peripheral sclerosis. The hemoglobin content (Dare) was 36 per cent; the erythrocytes numbered 2,540,000, and the leukocytes 7,000. The urine showed a specific gravity of

1.014, albumin 1, and many red blood cells. The plasma sodium chloride was 495 mg. for each 100 cc.; the carbon dioxide combining power of the plasma was 64 per cent, but other observations were not suggestive of high intestinal toxemia, and gastric retention was not present.

The patient improved somewhat for about ten days, when he contracted acute parotitis, followed by otitis media, mastoiditis, cellulitis of the face and bronchitis; he died from uremia on March 12, sixteen days after admission. The blood urea had risen to 346 mg., creatinine to 17 mg. and plasma phosphates to 8.3 mg., but the blood pressure had remained normal, the highest recorded pressure being 138 systolic and 85 diastolic (fig. 1). Edema had not been present, and there were not any signs of cardiac collapse until the last day of the illness. The clinical diagnosis was chronic glomerular nephritis with the terminal conditions mentioned.

The observations at necropsy were as follows: (1) chronic glomerular nephritis; (2) adhesive pericarditis; (3) acute bronchitis, with edema and

Fig. 2.—Section from kidney showing marked glomerular injury; × 140.

congestion of the lungs and small pulmonary abscesses; (4) cellulitis of the face, parotitis, otitis media and mastoiditis; (5) old hyperplastic tuberculosis of the hilum lymph nodes; (6) adenomas of the suprarenals; (7) adenomas of the right lobe of the prostate; (8) slightly enlarged spleen (weight 320 Gm.), and (9) diverticula of the urinary bladder with trabeculation of the wall. The changes of chief interest in view of the clinical course were in the kidneys, heart and blood vessels.

The left kidney weighed 102 Gm. Its capsule was slightly adherent, and when stripped, left a granular surface. The remnants of fetal lobulations were fairly well marked, and numerous small petechial hemorrhagic areas were seen beneath the surface. Cut sections showed a thinned cortex with many petechial hemorrhagic areas throughout the pale tissue. There was a small cystic area in the lower pole measuring 5 by 3 mm. and filled with yellowish, gelatinous, translucent material. The right kidney weighed 120 Gm. and showed more prominence of fetal lobulations. There was a turkey-egg mottling due to areas of petechial hemorrhage in the cortex and small, yellow, firm, raised nodules. On

section, the cortex was thinned and the markings indistinct as in the left kidney. Abnormalities were not noted in either the pelvis or the ureter in either kidney.

Microscopic examination of the kidneys showed extensive chronic glomerular nephritis with secondary involvement of the tubules and marked interstitial changes (figs. 2 and 3). Most of the glomeruli were either partially or completely obliterated. Some were hyalinized, some hemorrhagic and some showed lobulation and crescent formations. Bowman's capsules were markedly thickened. The tubules were distended and some contained albuminous material. Extensive diffuse fibrosis was present throughout.

The pericardium was thickened and tightly adherent throughout. Edema of the fatty portion of the epicardium was present. The heart with some of the adherent pericardium weighed 340 Gm., and the true weight of the heart was estimated at a little over 300 Gm. The myocardium was pale brown. The mural endocardium and valves did not present notable lesions. The foramen

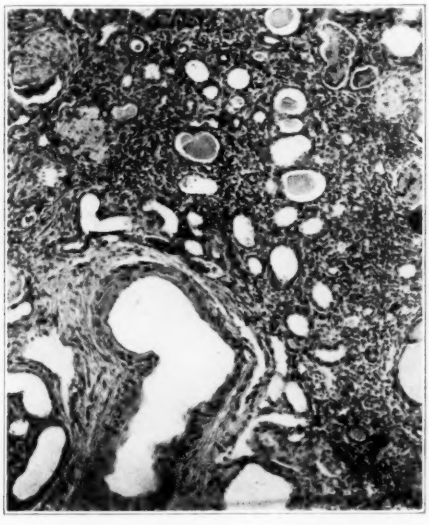

Fig. 3.—Section from kidney showing diffuseness of renal injury and the absence of sclerosis of renal vessels; × 60. See necropsy records.

ovale was closed, and the base of the aorta showed little if any sclerosis. The coronary vessels were of normal caliber and showed practically no sclerosis. The following measurements were made: aortic valve, 6.5 cm.; mitral valve, 10 cm.; tricuspid valve, 13 cm.; pulmonary valve, 6 cm.; depth of left ventricle, 7.5 cm.; thickness of left ventricle, 1.4 cm.; depth of right ventricle, 9 cm., and thickness of right ventricle, 0.3 cm.

On microscopic examination of the heart, the cells were found apparently normal in size and staining characteristics. The nuclei were regular and fairly even in size and shape. There was a slight increase in the amount of fibrous tissue, particularly in the proximity of the blood vessels, and in these situations a small collection of lymphocytes and a slight perivascular infiltration. The endocardium was slightly thickened. There was no fatty degeneration.

Very little arteriosclerosis was present. In the vessels examined, the intima and media were of almost normal thickness and arteriosclerosis was graded 1—. One of the renal vessels is shown in fig. 3.

CASE 2.— A boy, aged 15, came to the Mayo Clinic on Jan. 7, 1925, because of an abscess of the right axilla, anorexia, weakness and malaise. He had had scarlet fever at the age of 9, influenza at 10, tonsillitis at 12, and furunculosis at 13. One month before admission to the Clinic, he had felt malaise and weakness and had stopped going to school. A week later, his throat became sore and the cervical lymph nodes enlarged. In a few days, a painful, tender lump was noted beneath the right arm. This mass was incised and drainage established, but the patient gradually became weaker and drowsier.

The patient appeared stuporous and anemic, and the breath had a uremic odor. Edema was not present; the blood pressure was 112 systolic and 70 diastolic, and a retinal examination did not reveal anything abnormal with the exception of slight anemia. The heart was not hypertrophied and seemed normal; the urine showed a specific gravity of 1.009 with much albumin and occasional pus cells. The blood urea was 158 mg. and creatinine 6 mg. for each 100 cc. The phenolsulphonphthalein test showed only a faint return of the dye in two hours. The hemoglobin content (Dare) was 57 per cent; the erythrocytes numbered 2,900,000 and the leukocytes 23,300. The abscess in the right axilla was still draining pus, but apparently the drainage was not free; so another incision was required. The local condition improved rapidly

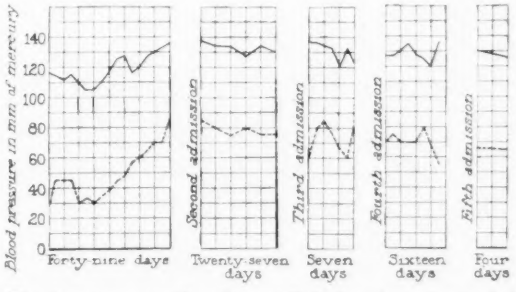

Fig. 4.—Blood pressure readings in case 2 during the entire period of observation. Note that systolic pressures higher than 140, and diastolic pressures higher than 90 were not observed. Note high pulse pressures. The continuous line indicates systolic pressure, the broken line, diastolic pressure.

following this, but the patient gradually became more toxic and manifested severe acidosis. The blood urea reached 220 mg., the creatinine 17.2 mg., and the carbon dioxide combining power of the plasma dropped to 15 per cent. However, under intensive treatment the patient improved remarkably and was dismissed from observation on Feb. 25, 1925. The blood urea at that time was 53 mg. and the creatinine 4 mg.; the urine showed only traces of albumin, and the blood count was practically normal.

During the entire period in the hospital, the blood pressure was recorded nearly every day, and the highest systolic pressure was 138 and the highest diastolic pressure 88. The pulse pressure was higher than normal most of the time, especially during the first few weeks when the patient was acutely ill (fig. 4). The eyegrounds remained normal.

The patient was readmitted to the hospital on May 12, 1925. He was feeling well and looked strong and healthy, but there was evidence of renal insufficiency with a low specific gravity of the urine; albumin 2. The blood urea was 75 mg. and creatinine 5.5 mg. Fundal and cardiac observations were negative. The systolic blood pressure was 138 and the diastolic 88, which was the highest pressure recorded during the twenty-seven days that the patient was in the hospital.

The patient was dismissed improved. He returned again on July 22, 1925. He seemed to be well and strong, and the only changes observed since the last examination were that the blood urea content had risen to 127 mg. and the creatinine to 5.6 mg. The highest recorded blood pressure was 138 systolic and 60 diastolic. The pulse pressure was again somewhat increased.

When again admitted, Sept. 10, 1925, he seemed to have failed considerably. Anemia was marked. Blood urea was 134 mg. and creatinine 5.2 mg. The whole picture was classical for asthenic uremia, except that as before, the fundi seemed normal, the blood pressure was 128 systolic and 70 diastolic and evidence of cardiac hypertrophy or weakness was not present. During sixteen days in the hospital, the highest recorded systolic pressure was 138, at which time the diastolic pressure was 66. The highest pulse pressure was 72.

Finally the patient came back on March 19, 1926, in terminal uremia with severe anemia and acidosis. The blood urea was 459 mg. and creatinine 19.6 mg. Hemoglobin content (Dare) was 30 per cent; the erythrocytes numbered 1,490,000, and the carbon dioxide combining power of the plasma was 20 per cent. There still were not any retinal changes nor any evidence of cardiac hypertrophy. The systolic pressure was 130 and the diastolic 65. The patient wished to return home. He died there ten days later. Postmortem examination was not performed.

COMMENT

Case 1 presented considerable difficulty in diagnosis when the patient was admitted to the hospital. Because of the normal fundi, cardiac condition and the blood pressure, together with the high blood urea content, moderate lowering of the plasma sodium chloride, slight tendency toward alkalosis and a questionable history of malignant neoplasm, high intestinal toxemia with associated renal insufficiency was at first suspected. The absence of gastric retention, however, the rapid drop of the carbon dioxide combining power of the plasma, the extremely high blood creatinine and the results of urinalysis pointed to primary nephritis. The insidious onset and slow development without edema indicated chronic glomerular nephritis rather than an acute or subacute type, and this diagnosis was definitely confirmed at necropsy. Chronic pyelonephritis had been carefully considered, but the history and observations made this possibility unlikely.

In case 2 the blood pressure readings were slightly higher than normal on a few occasions for a boy, aged 15 or 16, but these observations were infrequent, most of the many blood pressure readings recorded during fourteen months of intermittent observation being within normal limits. On many occasions the blood pressure during the early part of this patient's first admission was decidedly below normal, which was probably due to sepsis with acidosis and exhaustion, but these factors had no bearing on later examinations when the patient seemed to be strong and well. He had been working on the farm prior to his second and third admissions, and had returned on these occasions because he had been requested to do so. The pulse pressure, however, was considerably increased during his first admission. This may also have been associated with his exhaustion, since it was less pronounced on subsequent examinations.

CONCLUSION

Rare cases of severe chronic glomerular nephritis terminating in uremia may occur without hypertension, cardiac hypertrophy or retinal changes. The appreciation of this possibility aids in the correct diagnosis of these unusual cases and adds important data to the study of hypertension and nephritis.

CORRECTION

In the article by Drs. Edward H. Mason and Howard H. Mason, "Effect of Ultraviolet Light on Oxygen Consumption and on Total Metabolism" (ARCH. INT. MED. **39**:317 [March] 1927), the summary of blood counts on page 327 should follow the data concerning case six, rather than those concerning case three.

Book Reviews

TRANSFUSION OF BLOOD. By HENRY M. FEINBLATT, M.D., Assistant Clinical Professor of Medicine, The Long Island College Hospital, Brooklyn, N. Y.; Hematologist to the United Israel-Zion Hospital; Pathologist to St. Peter's Hospital; Assistant Attending Physician to the King's County Hospital; Hematologist to the Shore Road Hospital. Cloth. pp. 137, with 24 illustrations. New York: The Macmillan Company, 1926.

This book is an excellent and careful critical survey of the subject of blood transfusion as it stands today. The early chapters give a complete historical résumé of the steps in the development of blood transfusion, with particular reference to physiologic considerations.

A concise and clear description of blood groupings, donors, indications for transfusion and the dangers resulting from transfusion is considered in separate chapters.

One wishes that the author had devoted more time and space to a discussion of the various methods of transfusion, especially considering the citrate methods. His own method is given in great detail and might lead the reader to believe that this method is the one of choice, instead of being one of the direct methods.

The final chapters are short and concise and are devoted to blood transfusion in children and autotransfusion. In the chapter on blood transfusion in children, consideration is given to the body weight in calculating the average amount given for a single transfusion. The author states that it is rarely necessary to utilize the superior longitudinal sinus, as one is seldom unable to pierce a child's vein by properly cutting down on it. Full details of both procedures, however, are given. Intraperitoneal transfusion is fully discussed in both the direct and citrate methods and, therefore, furnishes an additional means of performing blood transfusions under conditions in which the veins are so small and collapsed as to be entirely inaccessible.

Great care has been taken in carefully going over and sorting out the literature, and an extensive bibliography of both foreign and American contributions is included, based largely on the author's personal experience and views.

KIDNEY DISEASE FROM THE PHYSICIAN'S POINT OF VIEW. By ROLFE FLOYD, M.D., Junior Attending Physician and Pathologist at the Roosevelt Hospital. Cloth. Price, $2.50. Pp. 181. New York: Dougherty.

In the preface to this book, it is stated that its purpose is to bring together in short compass, information which the medical practitioner needs for an intelligent understanding of kidney disease — it is largely a statement of the work of others. Its contribution consists in the attempt to gather and digest as much information as possible, and to present it in concise, intelligible and usable form. Careful study of the book convinces one that the author has spent much effort, has kept to the object set forth in the preface and has done well. However well informed one may be concerning kidney disease, he could hardly fail to profit by a study of the material presented here, and the author's keenly critical and analytic discussion of it.

The classifications of nephritis, with reasons and lack of reasons involved, are well presented. The works of Delafield and of Volhard and Fahr are considered at length. A fairly severe criticism of "nephrosis" as an additional class of kidney disease is well supported by the author's analysis of the information available concerning this subject.

Excretion of salt and its disturbances constitute an interesting and instructive chapter. To those not entirely familiar with the value of chemical studies of the urine and blood in persons with nephritis, this is especially recommended. There is, of necessity, overlapping of subjects when chemical studies bring in discussions of edema, dropsy, uremia and hypertension; but these are all handled with the clearness that could come only from one who has the known facts concerning them well in hand.

Remembering the object of this book, and even considering how rapidly books become out of date, it is a pleasure to recommend it as a useful addition to any physician's library.

LIFE INSURANCE MEDICINE: A STUDY OF SOME OF ITS PROBLEMS AND THEIR RELATION TO CLINICAL MEDICINE. By Members of the Medical Department of The New England Mutual Life Insurance Company. Volume 1. Cloth. Pp. 219, with numerous tables and charts. Boston: New England Mutual Life Insurance Company, 1926.

To read this book is convincing proof that Life Insurance companies can and will write at least one chapter of "Medicine." The life insurance business has developed into one of the great commercial enterprises of our time, and naturally has accumulated a tremendous amount of certain types of invaluable information, specially applicable to many problems in preventive and clinical medicine. The value of statistics and data depends on their source, their accuracy and the honesty and intelligence of their interpretation, and there is no source from which the volume is so great, intelligent experience in their use so available or where there is less excuse for dishonesty of interpretation as the great mass of information accumulated by life insurance companies. It is true that they deal largely with selected groups, but comparisons are made with other groups, with census figures and other statistics. It is already clearly shown that gains in "expectation of life" have been largely limited to that group of diseases classed as infectious, while in those classed as circulatory, there has been a distinct loss. One interesting hypothesis is formulated in this connection, to wit: "The incidence of circulatory disease is in inverse relation to the amount of physical exercise which the group takes in the open air and, other things being equal, it is in direct relation to the amount of nervous and mental strain." Often the question of acceptability of a risk is decided on the result of a simple single test, and practical experience has justified this method of selection. Perhaps no better opportunity exists for the recognition and study of early signs and symptoms of disease than a careful examination of large numbers of applicants for insurance.

Eight extensive papers are presented on such varied subjects as preventive medicine, periodic health examinations, glycosuria, hypertension and longevity, the creatinine content of the urine and others. An extensive bibliography is appended to each chapter.

PNEUMOCONIOSIS (SILICOSIS): A ROENTGENOLOGICAL STUDY WITH NOTES ON PATHOLOGY. By HENRY K. PANCOAST, M.D., Professor of Roentgenology, University of Pennsylvania, and EUGENE P. PENDERGRASS, M.D., Associate Professor of Roentgenology, University of Pennsylvania. Cloth. Price, $4. Pp. 186, with 23 illustrations. New York: Paul B. Hoeber, 1926.

This is an elaboration of an article dealing with the roentgenologic aspect of pneumoconiosis which was published by the authors in the Journal of Roentgenology and Radium Therapy in November, 1925. It is here presented in the form of a monograph and deals particularly with roentgen-ray studies of various types of the disease. There are chapters devoted to dusts, dusty occupations, disease and preventive measures. There are numerous reproductions of radiographs which are well chosen, are printed on good paper and have

excellent explanatory legends. The authors classify the disease roentgenologically into three stages; the first stage is characterized by a definite increase in the prominence and extent of the shadows of the hilum of the central zone, a thickening of the trunk shadows of the mid zone and an increased prominence of the linear markings of the peripheral zone; the second stage is characterized by a typical mottling throughout the lungs, caused by small fibrotic nodules varying greatly in size from that of a pinhead to that of a pea, more or less symmetrically arranged. There is often some interference with diaphragmatic excursions particularly the inner portions; the third stage is characterized by a diffuse fibrosis of varying type and degree, at times even "massive," with emphysema, pleural thickening, dense fibrous bands often wide and connected with marked deformities of the diaphragm and associated with restriction of diaphragmatic movements. The differential diagnosis from tuberculous conditions is discussed. A partial but well selected bibliography is appended.

MODERN MEDICINE, ITS THEORY AND PRACTICE, IN ORIGINAL CONTRIBUTIONS BY AMERICAN AND FORIGN AUTHORS. Edited by SIR WILLIAM OSLER; ed. 3 revised. Re-edited by THOMAS MCCRAE, assisted by ELMER H. FUNK. Volume 2. Pp. 891 with illustrations. Price, $9. Philadelphia: Lea & Febiger, 1925.

This volume includes the discussion of diseases of doubtful etiology; those caused by protozoa, spirochetes and animal parasites; diseases due to physical, chemical and organic agents; and deficiency diseases. Revision of all of the chapters has brought the subject matter up to date. This has been done for the most part by the original contributors. The former chapter on syphilis by Osler has been revised by Lewis A. Conner, and the one on yellow fever by Carroll has been rewritten by Thomas McCrae. The authoritative character of the original work is retained throughout. Of special interest are the chapters on smallpox by Beardsley, on vaccination by Dock, on measles by Ruhräh, on typhus fever by McCrae, on malaria by Craig, on syphilis by Osler, Churchman and Conner and on diseases caused by animal parasites by Stiles. The chapters devoted to deficiency diseases include the important discoveries of the past few years. Although definite progress has been made in this field, much remains obscure. The revised chapters naturally reflect the incompleteness of our knowledge of these subjects.

This volume, indeed the complete work, should find a place in every medical library.

IMMUNISATION LOCALE. By A. BESREDKA. Pp. 252. Price, 20 francs. Paris: Masson and Cie, 1925.

In this monograph Besredka presents a fascinating survey of the work of his school in its relation to local immunization. Incidentally, he has developed at some length his views on many phases of natural and acquired immunity. Starting from the observation that in staphylococcus, streptococcus and anthrax infections physicians deal primarily with a skin infection, and that with cholera, dysentery and typhoid they deal with a gastro-intestinal infection irrespective of the avenue of infection (intravenous, intraperitoneal, subcutaneous or by mouth), he develops the thesis that the protective immunization against these infections should be developed chiefly in the respective tissues. For immunization by mouth he has insisted repeatedly on the use of bile in preparing the way so that proper contact may be made with the bacteria ingested and the mucous membrane which is to be immunized. Interesting is his conclusion that the humoral antibodies play a relatively minor rôle in protection against disease, an opinion that has won much ground among immunologists in general, but which still seems novel to many clinicians.

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